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THE TREATMENT OF MALARIA

By JOHN COWAN and ROBERT H. STRONG

It has been our fortune to spend most of the last three years in Egypt or Palestine, for the greater part in Alexandria, and to be concerned with the treatment of large numbers of men suffering from malaria. During 1916 the incidence of this disease among the troops was slight, but in the autumn of 1917 a large number of cases appeared in the hospitals. These men had, as a rule, been infected outwith Egypt, in Macedonia or in Italy. A few had been infected in India, Mesopotamia, East Africa, and elsewhere. As winter approached, a new source of infection became manifest in Palestine, and though in the early months of 1918 the numbers decreased, they rose again in the autumn, and in October–November a very large proportion of the patients in hospital were suffering from this disease.

In the spring of 1918 we began to realize that the treatment of malaria was unsatisfactory. It was true that the mortality was small, but relapses were frequent and convalescence was prolonged. Our attention was thus attracted during the past year to this disease in particular, in the wards and elsewhere. We have investigated the literature of the subject so far as it has been possible to do so, and we have obtained much information from our colleagues, whose service has extended to every part of the globe. The present article contains our conclusions on the matter.

We have to acknowledge, with thanks, the information and assistance that has been given us by W. L. Baker, C. B. Blackburn, H. A. Bransbury, R. J. Cahill, W. Campbell, J. H. Conway, O. C. P. Cooke, J. M. Darling, J. C. Dunn, G. B. Eadie, A. R. Ferguson, W. H. Fisher, H. Fairley, C. A. Gill, J. W. C. Gunn, H. A. Haig, R. M. Knox, E. C. Lambkin, P. S. Lelean, F. D. Lumb, J. W. Mackenzie, L. M. V. Mitchell, C. W. O'Brien, T. T. Rankin, K. H. Reed, R. W. Reid, W. T. Ritchie, A. L. Sharpin, C. E. Silvester, G. E. F. Stammers, E. Bellingham Smith, R. S. Taylor, J. Thomson, F. D. Walker, J. E. Willmore, J. B. Yeoman.

There is an extraordinary diversity of opinion with regard to the amount of quinine required to cure a malarial infection. Leaving out of account the treatment during the acute stage, and considering only the course recommended in order to prevent the occurrence of relapse, it is found that Manson recommends a daily dose of gr. 15–20 for a week, with once a week a saline aperient followed by a single dose of gr. 15; the latter being continued for 6–8 weeks. Or

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alternately gr. 5 daily for three months. He also gives a month's course each spring and autumn for two years. Castellani and Chalmers recommend gr. 20 daily for a week, gr. 10 for two weeks, and gr. 5, with a double dose once a week, for three months. Osler recommends gr. 20–30 for the first three days, continuing the remedy in smaller doses for 2–3 weeks. Craig gives gr. 15–30 for three days after the fever has subsided, gr. 15 every other day for a week, and then every sixth day for at least two months. But all writers are agreed that relapses are extremely frequent, and an essential feature of the disease, though they might perhaps be more accurately described as an essential feature of an imperfect cure.

A series of papers by Col. Sir R. Ross and Capt. D. Thomson have thrown some fresh light upon the problem. Their work was undertaken in Liverpool, before the war, and was based upon a new procedure, namely, the *quantitative* estimation of the parasites in the blood. Some 200 cases were examined, many of them on successive days for long periods, and even on several occasions on the same day, and the facts were correlated with the amount of quinine which was given. The investigation has thus a very special value, as the conclusions are based upon specific data, and not upon a general impression formed from isolated observations over a period of years.

There are several points in their work to which we would draw attention.

(1) It requires a considerable number of asexual parasites per *c.mm.* of blood to produce an attack of fever. In Case 17, for example, an infection with *Plasmodium falciparum*, the number of parasites present on successive days was: 5,250. 380. 2,837. 336, 288, 184, 60. 36, 55, 12. 1,750. 360, –, 8, –, 12, –, –, 28, 60, 1,325, 1,250, –, 8, –, –, –, –. The figures underlined indicate the days on which fever was present.

Average figures in a series of cases show the connexion still more clearly. 43 pyrexial periods were studied; in every case, with one exception, the fever was associated with a comparatively large number of parasites. 46 apyretic periods, on the other hand, were associated with a comparatively small number of parasites. No marked rise in the number of parasites occurred without corresponding fever. The contrast between the average number of parasites on febrile and afebrile days is striking.

	Febrile days.	Average number of parasites per day.	Afebrile days.	Average number of parasites per day.
P. vivax	30	4,535	68	125
P. falciparum	97	13,607	83	461

(2) The absence of fever is not necessarily an indication that parasites are absent from the blood, and cannot be assumed to be an index of the cure of the infection.

(3) The general conception that parasites disappear between relapses is erroneous, for they were found in small numbers in 59 of 95 apyretic days. 'The parasite curve, at its height during a pyrexial period, generally falls very rapidly at first and more slowly later, and tends to reach its lowest about half-

way between two pyrexial periods. At this point it may or may not remain above the detectable point. After this it was observed to begin mounting, slowly at first, until when it reached the pyrogenic limit another pyrexial period commenced. All this is scarcely compatible with the speculation that the apyrexial periods are due to the abrupt death of the asexual plasmodia, or to their conversion into "resting stages", &c. Nor do such speculations appear to be necessary. It is easy to see that the survival of comparatively small numbers of the asexual forms will suffice to keep the infection alive, not merely for the short periods observed by us, but for relapses of "long interval", and for months or years.'

It is an error to assume that relapses occur by parthenogenetic development of the asexual forms from the sexual parasites. Relapses occur in cases where gametes are absent as well as in cases where they are present. The evidence points to the development of the crescent bodies from the asexual parasites, their development taking from 8 to 10 days; to their survival for only a few weeks; and to their persistence in the blood from constant replenishment by new formation, rather than to their longevity or resistance to quinine.

The sexual parasites are necessary for the continued propagation of the malarial parasite, and can only fulfil their function when ingested by a mosquito. Any condition which makes the life of the asexual parasites within the human host precarious tends to induce or further the formation of gametes. But these are formed from asexual parasites, and their presence predicates the existence of asexual parasites in the body a week or two previously. The administration of quinine in sufficient doses is followed by the diminution in number, or the disappearance, of gametes from the blood, but the curves of the asexual and sexual forms do not coincide, the latter succeeding the former, and the gametes only disappear two or three weeks after the disappearance of the asexual parasites.

The successful treatment of malaria cannot then be gauged by the presence or absence of fever, *for the infection may continue alive, though latent, after all symptoms have disappeared.* The mass of the infection is lessened to such a degree that the obvious symptoms disappear, but the infection itself persists, and, given favourable circumstances, may be rapidly augmented and so produce a relapse.

It is well known that excessive fatigue, chill, or gastro-intestinal or other disturbances may provoke a relapse in latent cases. The removal of such conditions is not infrequently followed by the disappearance of the malarial symptoms, and may follow simple rest in bed, with its avoidance of exertion and chill, quite apart from the administration of quinine. The fever disappears and the parasites may also even disappear from the blood, but their destruction has not been accomplished, and sooner or later they reappear, and an attack of fever succeeds.

Sir R. Ross and D. Thomson have studied the reaction to quinine in these ways. They found that the administration of quinine in isolated doses exaggerated this tendency of the parasites to disappear, and lengthened the

period of their absence, but relapse inevitably ensued. (Cf. their charts 9 and 10.) Quinine in doses of gr. 5 daily and in gr. 30 doses for 8 days proved equally inefficient, and the minimum dose which seemed effective was gr. 30 continued for 21 days. They do not maintain that this dose is invariably effective, but the results obtained by this treatment were infinitely superior to those obtained otherwise, and relapse occurred but once during the period of observation.

The essential difference in the treatment recommended by these writers from that of other authorities lies in *the continuance for more than a fortnight after the symptoms have disappeared* of the dose required to subdue the symptoms.

The use of quinine as a prophylactic by persons who are exposed to malarial infection has little evidence in its favour. The fallacies of statistics are of course notorious, and it is difficult to confine the issue to the point which it is desired to investigate. The Indian figures, for example, are based in large measure on data obtained from populations the subject of latent malaria, rather than virgin; and populations who are likely to be infected during the leave season, when quinine is not taken regularly.

Major Gill's paper must therefore be disregarded, for, although the health of the troops under his charge at Muscat was greatly improved by the administration of quinine, his population was already infected.

Col. Lelean's paper, based upon the statistics of the Indian jails and Indian Army, is also tainted by the same fallacy. From his analysis of the general admission, death, and case mortality rates in the jails, he concluded that, instead of a reduction, there had actually been a considerable increase in the prevalence of malaria during the quinquennium 1905–10. He quotes the figures of experiments upon groups of 130 men in the jails of Peshawar and Dera Ismail Khan in the years 1908–9.

	Malarial admission rates per mille.
(1) Taking no quinine	476
(2) Taking gr. 5 daily	476
(3) Taking gr. 15 twice weekly	430

Experiments were made in Saharanpur and Gorakhpur in 1908. In the former the malarial admissions declined from 516 to 336, but in the latter rose from 227 to 233, while it is 'evident that the general hygiene has improved to such an extent in these jails that the total admissions from all causes other than malaria have diminished more rapidly than those for malaria; in Saharanpur to the extent of 16 per cent., and in Gorakhpur to the extent of 21 per cent.'

The results obtained with prophylactic quinine in the 7th Division in 1909 'presented so overwhelming a case against its use' that similar data were collected in 1910. The results were better, but by no means satisfactory, the malaria admission rate per mille per annum only diminishing in Delhi from 1,144 to 796.

Capt. Stott's study is perhaps the most conclusive, though open to the same fallacies, and referring to only limited numbers of men.

The 91st Punjabis were stationed in Fort Dufferin in Mandalay in 1911, and

an epidemic of malaria occurred. The admissions to hospital in July, 1911, reached 250 per mille, though prophylactic quinine in gr. 10 doses twice weekly had been instituted on 22.6.11. 'I therefore determined to try the administration of the drug to the odd halves of each double company only, and to use the even halves, who would receive no prophylactic quinine at all during the whole period of the trial, as a means of control.' Gr. 15 were given thrice weekly from 1.10.11 to 15.2.12. Gr. 10 were given thrice weekly from 20.4.12 to 30.9.12. During the two intermediate months, which form part of the non-malarial season in Burma, no prophylactic quinine was administered. As a result, it may be stated that out of each 500 men taking the drug for ten months in the year *one* was saved from an attack of fever. The rate of primary admissions to hospital per mille was 43·2 in the quinine group, and 45·8 in the no quinine group.

Stuart's paper is based upon the results obtained in American troops stationed on the Isthmus of Panama. His population was largely virgin, but the period of the experiment was short.

A sudden influx of troops led to their being quartered in camps which were known to be unsatisfactory, and quinine was in consequence given daily to the men. At Camp Diablo there were 200 men who had been on the Isthmus for six months or more, and 250 new arrivals. On 26.6.08 a daily dose of gr. 5 was commenced, which was increased to gr. 10 thirteen days later, as the early dose proved insufficient. In a month sixty-five men were admitted into hospital, of whom twenty-four were 'old' inhabitants of the Isthmus.

At Mount Hope there were 450 new arrivals. On 27.6.08 a daily dose of gr. 5 was instituted, which on 28.6.08 was raised to gr. 10. In sixteen days seventy-two men were admitted into hospital, and the camp was then closed.

At Camp Elliott, with 450 new arrivals, the conditions were more favourable, and quinine was given in the same doses as at Camp Diablo. No case of malaria occurred until the Mount Hope men were transferred to the camp. Twenty-three cases occurred between 16–31.7.08, with but few exceptions among the men who had been transferred from Camp Hope.

During the discussion which followed the reading of this paper objection was raised against the use of prophylactic quinine on the ground that it acted simply as a chemical agent in destroying the parasites, and had no antitoxic or reparative action upon the tissues. It could thus only be active at a definite strength, and the blood content should be the same whatever the number of parasites in the blood. *The prophylactic and the curative doses were in consequence the same.*

Carter has used prophylactic quinine in Panama in doses of gr. 3–5 daily. He gives no statistics, but states that he considers it to be a valuable adjuvant in the prevention of malaria.

Nocht and Werner reported the results obtained in Brazil, where 3,000 workmen were employed in an intensely malarious region. The workmen, who were compelled to take quinine, suffered but slightly, whereas their families, who refused to take it, were decimated by the disease. The men took gr. 7·5 every

third day from February to September. The results at first were satisfactory, but in the latter month some cases of malaria occurred. The dose was therefore given every other day, which at first proved efficacious, but in November the attacks recurred, so the dose was given daily.

Indian experience (Reviewer) has shown that though Europeans living in malarial districts in time develop immunity, this is only relative, and may fail before a massive infection or a deterioration of the general health from exposure or fatigue.

Treadgold's paper contains an analysis of some 200 papers. The large majority of these writers, however, give no details of their experience, or made no use of controls, so that only thirty-four papers were worth consideration. Of these twenty-six were in favour of quinine and eight against it. Further investigation revealed a difference in the nature of the material examined, as twenty-three writers were considering the effects on the *inhabitants* of a malarial area, and eleven the effects on an *immigrant* population. In the former group 100 per cent. approve the procedure. In the latter, only 27·2 per cent. There is thus apparently a marked difference in the action of the drug on infected and on virgin populations.

Treadgold himself has no faith in the value of prophylactic quinine. His personal experience was concerned with an infected population, troops who had served in Macedonia during the summer of 1916. In the spring of 1917 he examined the blood of 456 men who were on duty at the time. 141 (25·8 per cent.) showed parasites in their blood. All these men were taking quinine at the time of examination. 63 had never suffered from malaria. Of these five (7·9 per cent.) were infected.

Capt. F. D. Walker's experience in Brazil and Bolivia, while in medical charge of the Bolivian Survey in 1912–13–14, may be mentioned. The expedition was travelling through an intensely malarious district. The English and Bolivian officers (twelve to thirteen) habitually took a daily dose of gr. 5–10 quinine, while those of the Brazilian Commission did not do so. The health of the first group was good, and only one individual had an attack of malaria during the twenty-four months spent in South America, though several are known to have had attacks subsequent to their return to England. The exception had refused to take quinine. Several members of the Brazilian party had to be invalided on account of malaria.

There is a widespread opinion that the continued use of prophylactic quinine renders the infection, if incurred, more difficult to cure. This point was raised by Capts. Blood and Sanderson at a meeting of the Alexandria Medical Society in January, 1917, as the result of their experience at the 17th General Hospital. Their paper was based upon the data afforded by 622 cases admitted into hospital in the late autumn of 1916, diagnosed malaria; 187 had the diagnosis confirmed by microscopic examination of the blood in Egypt.

On arrival in Alexandria it was noticed that, almost without exception, the cases of malignant infection were very anaemic, and had well-marked enlarge-

ment of the spleen and haemic bruits. They proved very resistant to treatment. As they had all had a daily dose of gr. 6–10 quinine for from three weeks to four months before their first attack of fever, its influence had to be considered. They quoted some figures of Stitt. In 1906, 398 marines served for about a month upon the Isthmus of Panama, during which time they received a daily dose of gr. 9 quinine. There was only an occasional case of fever during their residence, but as soon as they re-embarked and sailed north and the administration of quinine ceased, malarial attacks supervened, 215 occurring among 298 men. A daily dose of gr. 9 was thus insufficient to prevent infection, though sufficient to prevent an attack of fever.

The authors concluded that, though prophylactic doses might delay the onset of fever, they were in no way a preventive; that in patients who had taken it the onset of fever indicated the administration of larger doses of quinine than were necessary in men who had not had prophylactic doses; and that, when prophylactic quinine had once been instituted, it must be continued for an indefinite period.

Capt. Willmore thinks that primary attacks in persons who are not taking quinine are sharp, but readily amenable to treatment. In men who have been taking quinine the primary attack is less severe, but difficult to cure. The usual reason alleged is that the parasites in time become accustomed to, and relatively immune to, the drug.

A paper by Teichmann, a physician at a German 'Etappenlazarett' in Turkey, discusses the possibility of another explanation. The question was apparently raised on account of the failure of quinine prophylaxis in his area. Quinine being an alkaloid, one is justified in assuming by analogy (alcohol, opium) that the longer the period of administration the more readily it is destroyed in the body, and the less does it circulate freely, so that only a small portion of the dose encounters and attacks the parasites. The effective amount may be gauged by the estimation of the quinine content of the blood and of the urine, after intravenous injection. This method applied to groups of men 'accustomed' and 'not accustomed' to quinine showed that the quinine content in the former group was much less than in the latter. So that in those accustomed to quinine only a small fraction of the dose administered reached the malarial parasites.

The experiment requires to be repeated, and on the grand scale, before any definite conclusion is reached. An observation of D. Thomson suggests that in some cases at any rate immunity of the parasite may occur. A man was admitted into hospital on October 23 suffering from a double infection. The fever disappeared after three days, and gr. 30 were continued daily. On November 10 fever recurred. As no parasites were found in the blood, the quinine was stopped, but it was again started on November 14, as the parasites reappeared. On November 21 the fever still continued, so on November 22 an additional dose of gr. 30 was given intramuscularly, and gr. 12 methylene blue. On November 23 the fever disappeared and recovery ensued.

On the supposition that the quinine was not being properly absorbed by the digestive tract, the urine was examined, and found to contain gr. 16 quinine, about the usual amount, which showed that the blood-content should have been ample.

Another explanation has been suggested by Barlow, whose paper, however, we have not been able to procure. It is referred to by Treadgold, who accepts the theory as in harmony with the facts. 'Barlow, as the result of experimental work, thinks that quinine in therapeutic doses does not directly destroy the plasmodium, but tends to poison infected red corpuscles in such a way that they are more easily acted upon by the excretory products of the parasite. This results in its liberation before segmentation has taken place, and facilitates its destruction.'

But the available data on the whole seems to support Teichmann's theory.

It seems clear that quinine administered in small doses to a virgin community exposed to malarial infection has little effect in preventing infection, and may, indeed, be prejudicial by inducing a condition of affairs which renders the infection more difficult to eradicate; that the present treatment of malaria by 'diminuendo' doses is not satisfactory; and that the most plausible theory accounting for these facts is that the continued administration of quinine leads to a rapid destruction of the drug in the tissues, and hence to a diminished blood-content, too small to exercise any marked effect upon the disease.

The treatment of malaria, however, is not merely a question of the dose which is required. In general terms quinine is a poison. According to Cushny it affects the general nutrition of almost all forms of protoplasm, producing at first a transitory augmentation of its activity, followed by depression and by death.

In man the ordinary therapeutic doses as a rule do not produce harmful symptoms. But these may obtain in cases where large doses are administered, or in patients who are peculiarly susceptible to the drug. Transient disturbances of hearing and vision are most common, and are of little importance, but occasionally permanent effects are produced, probably from changes in the nerve-cells, leaving permanent deafness or blindness. Gastric disturbances may ensue, or cerebral symptoms such as confusion and depression with a sense of fullness or heaviness in the head, accompanied sometimes by an uncertain gait. There may be notable cardiac weakness with collapse, muscular weakness, apathy, and slow gasping respirations, and finally unconsciousness and respiratory failure.

Quinine, like every potent drug, must be used 'with brains'.

At the present day no one imagines that they *cure* disease with drugs. Even in surgical sepsis antiseptics have no miraculous action, and the ultimate recovery is due to the action of the fluids and tissues of the body upon micro-organisms whose vitality is at most merely lowered by such means. In septicaemia the same rule holds good, and the action of drugs upon such protozoal diseases as malaria,

syphilis, and amoebiasis, though more powerful than that in comparable bacterial diseases, is still minimal and incapable by itself of overcoming the disease. Aided by the natural processes, however, recovery ensues. Either by itself is insufficient; joined together, the victory is complete.

The treatment of malaria must be viewed in different ways according to the stage of the illness. At one period acute symptoms are present, which from their intensity immediately endanger the patient's life, and require energetic treatment with quinine in such doses as will at any rate reduce the mass of the infection to reasonable limits, even though the dose is so large that it is detrimental to the general health. At another stage the symptoms are trivial and not immediately dangerous to life, but they are recurrent. Here the general health requires special consideration, and the dose of quinine must be kept within the limits that are not harmful. In one stage the patient requires rest in bed and full nursing care. In the other continued residence in hospital is probably harmful, and an open-air existence with carefully graded exercise is more likely to produce the desired result.

In the early spring of 1918 it became apparent that the treatment of malaria in the E.E.F. was not satisfactory. The mortality was trifling, but relapses frequently occurred after dismissal from hospital. During the last three months of 1917, for example, 4,490 men were admitted into the Command Dépôt at Alexandria, and 11·5 per cent. required to be taken into the Reception Hospital on account of relapses. Many others had mild relapses which did not necessitate hospital treatment. During the next three months the results were worse: 3,442 malarial patients were admitted into the dépôt, and 26·1 per cent. were taken into hospital.

The bulk of these men had been infected outwith Egypt, and were admitted into the Alexandrian hospitals suffering from other than primary attacks, but they had all undergone treatment in hospital in Egypt. An investigation into the treatment of malaria in Egypt was therefore undertaken.

The treatment was largely based upon the memorandum on the treatment of malaria, compiled by the late Col. F. M. Sandwith, and circulated among the R.A.M.C. in 1916. In this it was recommended that gr. 30 quinine should be given daily during the fever, and for another week. During the second week gr. 20 should be given daily, and subsequently for three months gr. 10. The initial dose might be increased to gr. 45 if found necessary. In the main the treatment recommended was carried out, so that it was obvious that this routine was not followed by the desired results.

The possible causes of relapse were then examined.

(1) A common cause of relapse is re-infection. It was improbable that this was the case in Alexandria, for malaria is rare on the station, and only twenty to thirty cases occur yearly. At Mustapha, where the Command Dépôt was then situated, only three cases of malaria had occurred in the previous three years (Col. Stammers, Major Fisher). Anopheline mosquitoes are not numerous, though

there are many culicidae. Mosquitoes are most numerous to the south of the town, while the prevailing winds are from the north, and the bulk of the troops are camped in the same quarter.

(2) It is well known that privation, chill, severe exertion, excess, &c., are common causes of relapse. But these factors were not active among the troops at the Command Dépôt.

(3) During 1917, 2,001 positive examinations of blood-films were made in the laboratories in Alexandria. Of these 1,615 were benign tertian, 354 were subtertian, 3 were quartan, and 7 were mixed infections. In 22 cases the parasite could not be satisfactorily identified.

It is possible that different strains of parasites may vary in virulence. Major Fisher referred to this in his annual report, stating that the incidence of relapse among the patients at the Command Dépôt was much greater among men infected in Italy and in East Africa than among men infected elsewhere. He thought, too, that the Italian cases were more severe. But, on the other hand, the mortality was slight, and not so large as one would expect with a virulent infection. The malaria which occurred in Palestine in the autumn of 1918 was of a virulent type, and had an appreciable mortality.

(4) The influence of prophylactic quinine. We have already referred to this point. The Macedonian cases had had prophylactic quinine, but the Italian cases had none.

(5) The treatment during the primary attack.

On the whole the initial treatment ran on comparable lines. Doses of gr. 30 or more were given during the febrile stage. But only 7 of 26 officers used the continued treatment recommended by Sir R. Ross and D. Thomson, and of these only 3 retained the patients in their own hospital for the requisite period, so that their approved treatment was not necessarily carried out.

The Panama practice is similar to that of Ross and Thomson. Brem, of Colon, analysed a number of routine systems in use in his hospital, and contrasted the results. In A gr. 30 quinine were given daily in doses of gr. 10, at 0600, 0800, 1000 o'clock. In B gr. 30–40 were given in four-hourly doses. In C gr. 20 were given in gr. 10 doses at 06.00, 08.00. This system of administration was devised, as he found, on analysis of the time at which 532 paroxysms occurred, that 80·3 per cent. occurred at 12.00, 16.00, 20.00, the largest number, 43·5 per cent., at 16.00.

The duration of the febrile period under A and B treatment was approximately the same. With C the fever in subtertian cases was nearly one-third longer; in tertian cases, one-fifth longer; and in clinical cases one-thirteenth longer than was the case in the patients treated with A and B. Gr. 20 quinine were thus less efficacious than gr. 30.

Contrasting A and B, he found that the symptoms of cinchonism were more marked in A, but vomiting was less frequent, and intramuscular injections were less frequently required.

According to Stitt the routine treatment at Panama is gr. 45 daily for a week, or for 4–5 days after the fever has subsided, followed by gr. 30 for 10–12

days. 'In the treatment of malaria in our American employees it was observed by Dr. Weeks that when the liquid preparation of quinine sulphate, which is used, was given in doses of gr. 20 per day by the mouth, while acute attacks were often controlled, recurrent cases in large number followed at very short intervals later, and in the treatment of these larger doses were necessary. A routine of gr. 20 on diagnosis, and gr. 10 three times a day later, for at least ten days, was then established, and this we used for several years. This noticeably diminished the number of recurrent cases among the Americans, but not sufficiently among the more poorly nourished European labourers. Dr. Deeks then instituted a treatment of gr. 45 per day in three doses of gr. 15 each. This has practically eradicated recurrent malaria among the Americans, and to a large extent among the European labourers' (James).

On a survey of the facts it seems probable that the frequency of relapses in the E.E.F. was not due to reinfection or to privation. The Italian infection may have been peculiarly virulent, but the main causes were the use of prophylactic quinine in Macedonia, and an insufficient dosage with quinine in the primary attacks.

The routine treatment in the E.E.F. during the last six months of 1918 has been a daily dose of gr. 30 quinine, continued for at least 21 days.

Relapsing Malaria.

Malaria is a most protean disease. The incubation period varies, ranging from a few days to many months. The onset of symptoms, as a rule abrupt, may be subacute. In some cases, too, the disease is latent, and its relationship to symptoms is only established on examination of the blood, as the symptoms are not malarial. In acute disease of other origin its influence may be considerable, but unseen.

The symptoms which succeed acute attacks may be even more diverse than those of the primary illness. Any organ may be involved, the symptoms may be general or local, fever may be absent, and the diagnosis may be self-evident, or only established on the closest scrutiny. But in a general way the cases may be classified into three main groups.

In (1) the patients are manifestly *ill*, unfit for any form of service, and evidently requiring hospital treatment.

(*a*) An acute attack may be succeeded by recurring and serious symptoms. A boy of 19 was admitted into hospital suffering from a severe attack of subtertian malaria, the result of infection at Taranto during his transit to Egypt. The symptoms passed off in a few days, but the boy, who was a growing lad and looked delicate, was retained in hospital for further convalescence. Three weeks later, while still in the wards and under quinine, the ague recurred. He was again seriously ill for a few days. His general condition was not satisfactory,

and he was weak and ill. Three weeks later a third attack occurred, with again a deterioration of his general health, and the attacks continued to recur until his transference to England. The infection presumably was massive, and the resistance small.

(*b*) In another group the attacks are not severe, but they recur, and the patient's general condition does not improve to an extent that permits of his return to work. He becomes weak and anaemic.

(*c*) In the third group slight fever, reaching 99°-100° at night, persists, but is not associated with any of the symptoms usually met with in malaria. There are no rigors or sweats, but merely increasing debility and anaemia, and the fever may indeed be missed if the temperature is not taken.

In all these cases the disease is uncured, and urgently requires treatment. The men are *ill* in the medical sense, and the question of employment is never raised even by the most casual observer.

In group (2) the men are *not seriously ill.* They are often well nourished and fit, and capable of even considerable physical exertion. But they are liable to suffer from ague, and during the attacks are untrustworthy from the military standpoint, though the disability is of short duration. In quiet times they can be treated satisfactorily in their units, but their presence in the front line is an additional anxiety to those who are responsible. The men themselves do not suggest that they are seriously ill, or require any more treatment than rest in bed so long as they are fevered. The attacks are short and mild. In a day or two the men are fit for work.

In group (3) comes an intermediate class. The men are not ill, but they are *unfit,* and so comparable to convalescents from pneumonia, enterica, and the like. But they differ from these in that the infection is not cured, and in this respect resemble the amoebic dysentery carriers. Two features obtain: an uncured disease and general debility. The amoebic cases, who were so numerous in the spring of 1916, after the evacuation of the Peninsula, were almost exactly comparable; and those of us who were in Egypt at the time can well remember the difficulties which they occasioned.

These men suffer from attacks which, as a rule, are not very severe, but the fever lasts for several days, during which they are entirely incapacitated; and successive attacks gradually induce an increasing degree of anaemia and debility. They are quite unfit for service with a unit, and in the opinion of most physicians do not benefit from continued residence in hospital. Convalescence is at the best a very tedious process, especially during the hot weather.

The immediate causes of an attack of ague in an uncured patient are somewhat obscure. The essential feature, of course, is the presence of parasites in the blood, but their presence is not necessarily associated with active symptoms. One of our service, for example, was found to have crescents in his blood two years after he had returned home, and a like period after his acute attack. He was at the time in good health. Such instances can be multiplied indefinitely,

and are at present by no means uncommon in the E.E.F. It seems, therefore, that some additional factor is required.

The ocurrence of ague indicates a *successful* invasion by the plasmodium. The mere occupation of territory is not sufficient, the defence must be overcome. This result may be attained by an advance in such force that the normal resistance is overcome, or by the normal resistance being unduly weak. In either case the parasite multiplies indefinitely and achieves success. The primary attack is due to an advance in force. A relapse may be due to the arrival of reinforcements, or to weakening of the defence. In Egypt the former is unusual and the latter is the rule.

Anything that depreciates the health of the individual to a sufficient degree is thus capable of inducing an attack. The actual cause may be of varied nature. It may act directly—for example, an attack of influenza—or indirectly, loss of sleep reacting upon the nutrition, and so upon the resistance of the individual.

The experience of the last few months has shown some of the common causes in Egypt. Of these the most frequent are:

(1) *Chill.* This may arise in different ways. Exposure to cold, either in the day-time or at night; wet clothes, from rain or sweat; prolonged bathing; insufficient clothing; may all be the essential factor. Exposure to the sun, on sentry duty, acts in the same way.

(2) *Exertion.* If it is excessive, and produces exhaustion.

(3) *Digestive upsets,* whether associated with gastric or intestinal symptoms.

(4) *Venereal excess.*

(5) *Debility.* In the fifth year of the war the army as a whole, both at home and abroad—indeed the whole nation—is war-weary, though to a lesser degree than the other belligerents. In some the strain is chiefly physical, the men are stale and overtrained. In some the cause is mental, social business or other worries reacting upon the nutrition and resistant power. In some acute disease has been antecedent. The result, however, is the same. It is important to recognize its existence, and to endeavour to exorcise the evil demon by every means available.

(6) *Coincident disease.* Every effort should be made to ensure a perfect convalescence before the man returns to duty. An unfit man, if infected with malaria, is extremely likely to have a relapse.

The best treatment of relapsing malaria is its prevention. In our opinion, a full course of treatment at the time of the primary attack will prevent relapse in the large majority of cases. It is known that this desirable result can be attained in civil life, and though the exigencies of active service make the problem more difficult, these difficulties do not seem to be insuperable. But it must be recognized that the cure takes time, that it cannot be hurried, and that it requires prolonged treatment in hospital and command dépôts. If the field of

operations were free from infection the problem would be simple, but this is not the case in Palestine, so that one must take into account the possibility of re-infection. But we would emphasize the truism that a man who harbours a minimal infection is more likely to become fevered if a fresh infection occurs than one who from the malarial standpoint is virgin.

The treatment of relapsing malaria is the treatment of a chronic and *uncured* disease. The character of the infection, the general condition of the patient, and the previous treatment of the case require particular attention.

The first and most obvious indication is the prevention of the exciting causes of attacks. Here one at once encounters war conditions, which may or may not interfere. If this difficulty cannot be overcome, the *second-best* course must be adopted, and every endeavour made to enhance the health of the men before they are again exposed to unfavourable conditions. A fit man is more likely to remain fit.

Diet. The general nutrition requires attention. The men have always lost weight, and this must be restored if a good result is to be obtained. The digestion is often upset, and this may induce a return of fever, besides interfering with assimilation. The food ration has been reduced, and should be augmented, but one must remember that quality and quantity are not synonymous. Every effort should be made to assist appetite by variation in the dietary. Beer and stout are sometimes useful.

The continued administration of quinine and iron not infrequently affects appetite or digestion, and it is sometimes necessary to stop all drugging of this kind and to pay exclusive attention to the digestive tract. A simple alkaline bitter, some pepsin, or nitro-muriatic acid may be of more value than the specific drug. Sir Astley Cooper cured a debilitated syphilitic who had been poisoned with mercury, with beef and beer, and the same moral applies here. Arsenic, too, is an irritant, and should be given in courses of a few weeks at a time and then intermitted.

Exercise. An amount of exercise which would be beneficial to a healthy individual may be excessive for a debilitated man. Captain Lumb's experience is interesting. During the first month of treatment of the Loyal North Lancashire Regiment the exercise was reduced to a minimum, and only the necessary fatigues were performed. The men, though encouraged to play games, did not do so. During the second month they began to play football, and in the third month the majority played, though now training had begun. The only real test is that afforded by experiment, and the rate of progress necessarily varies with each individual. The rate, too, is slower than that usually adopted at command dépôts.

Climate. The Indian authorities consider that a change of climate has a very beneficial effect upon the subjects of malaria, and recommend a change to the hills after an attack. In relapsing cases the men are invalided to England.

We have no experience of India, but our experience in Egypt strongly

supports the contention. The climate of Egypt is by no means perfect. The hot months are enervating, and the majority of men lose weight in the summer. The winter months are cold, at any rate to the dweller in tents, and in both seasons the humidity at Alexandria is considerable. Residence in a house under peace conditions may not be a great hardship, but residence under service conditions throws a strain upon even the robust.

Our personal experience during the last three summers has convinced us that one cannot expect a satisfactory convalescence in men who are notably anaemic or debilitated, if they are retained in Egypt during the summer months. In the winter better results are obtained, but it is economical to invalid men freely to England.

Quinine. The treatment of malaria in Panama and in India is so different that one has difficulty in understanding how the difference arose. The Indian physicians have proved their worth in so many fields that one cannot ignore their methods, but on the other hand the results obtained in Panama are superior. The only obvious conclusion is that the disease differs in some respect in the two places.

On reflection such a difference at once appears. The troops, who in India form the bulk of the patients, are natives. They have from their infancy been exposed to infection; many have been infected in infancy; and reinfection has occurred from time to time. In Panama, on the other hand, the population is white, and virgin to malaria. It seems probable, too, that the Indians may possess some racial immunity to malaria.[1]

If this is so, a very important conclusion ensues. The treatment *of primary attacks should be based upon the experience of Panama, while the treatment of relapsing cases should be based upon the experience of India.* An intensive treatment should be adopted in the primary cases in the attempt to eradicate the infection. In recurrent cases such a procedure is not likely to be beneficial, and the minimum amount of quinine that will subdue the symptoms is more likely to secure the desired result.

We have already pointed out that quinine in the doses used in the treatment of malaria has effects that are not wholly innocuous. The drug is a poison and affects the nutrition of every form of protoplasm. There is some evidence, too, that its continued use induces a relative loss of its specific properties. The preventive dose is large and requires augmentation after prolonged use, while in men who are exposed to repeated infection and repeated attacks of malaria the curative dose becomes progressively greater as the years go by.

Quinine poisoning may be acute or subacute. The degree varies according to the personal idiosyncrasy. Aural, gastric, cerebral, visual, and cardiac symptoms may occur. In blackwater fever the administration of quinine is generally condemned, even in cases where malarial parasites are present in the blood. In some malarial patients it seems to induce haemoglobinuria.

[1] Major G. B. Fleming tells us that Indian troops showed no immunity to East African malaria, whatever their reaction to Indian malaria may be.

But quite apart from these obvious effects of its adminstration its continued use seems to induce a general debility. It is said at Salonika that the incidence of malaria among the officers is less than that among the men. And, though there are many differences in the conditions of life in the two groups which offer a possible explanation, it is to the smaller amount of quinine taken by officers that the latter ascribe their relative immunity. The witness is unskilled, but the unanimity of opinion is striking.

In a general way we have been impressed with the same idea. In some cases men have taken quinine for months and even for a year. And although it is probable that the dose has been small, and more intermittent than stated, the total amount has obviously been considerable. The *first* point in such cases is to ascertain the amount of quinine that has been taken, and thus gauge in some measure the degree of *quinine intoxication.*

We have already referred to Treadgold's paper on malaria at Salonika, but some further details may be quoted here. He examined the blood of 456 men who were at the time serving with their units, and had served in Macedonia during the previous summer. Forty per cent. of those who had had fever during the preceding three months showed parasites in their blood; 17·2 per cent. of those who had not had fever within three months were infected, and 7·9 per cent. of those who had never had fever! A number of these men were taking quinine at the time of the examination, and the men *who were taking the smallest doses showed the fewest infections.* His figures, however, are small. He concludes: 'So far as the Allied Armies are concerned, there is every reason to suppose that quinine taken daily over periods of many months has increased the severity and the chronicity of the disease in a certain proportion of cases.'

Rawnsley thinks that quinine, in the doses usually given for prophylactic purposes, is quite useless, and in the larger doses is dangerous, as it masks the fever, though the men become anaemic with enlarged spleens and cardiac symptoms. He believes, too, that quinine should not be given for more than four weeks at a time, as signs of intolerance become manifest.

The interim report upon the treatment of malaria by Sir Ronald Ross is mainly based upon cases from Salonika. The majority were cases of benign tertian infection, and all were probably quinine sodden. The results of treatment by quinine were not satisfactory, as 27·7 per cent. (of 2,460 cases) were known to have subsequently relapsed.

Various forms of treatment were used, and the results obtained are contrasted. Six were designed as an anti-relapse prophylaxis, in the attempt to prevent relapses without effecting an absolute cure. Thirteen were short 'sterilizing' courses. Twenty-two were long 'sterilizing' courses.

The administration of quinine in any dose reduced the incidence of relapse, but not to a satisfactory degree. As a control 193 men were at first not given quinine, and 45·6 per cent. relapsed within twenty-seven days. Only nine of the different treatments gave less than 20 per cent. of relapses while the patients were under observation. Some of the results, too, are curious. In A 2

and A 4 the same amount of quinine was given, but in one case 15·2 per cent. relapsed, and in the other 8 per cent. The contrast between A 4 and C 17 is not very great, 8 and 10 per cent., while the dose in one was small and in the other large. In some cases the men were kept in bed, and in others sent for route marches, which suggests that the population was not always comparable. In general, however, the report suggests that in *quinine-sodden* men an intensive course of treatment is not uniformly successful, and that short courses do not sterilize. Any form of quinine treatment reduced the relapses from 46·6 per cent. to 25·7 per cent.

We are convinced, from our experience, that many cases of 'malaria' are really suffering from quinine poisoning. The amount of quinine that is administered is often large, and the smaller doses are continued for too long. In consequence, a condition of debility is induced, which, as its cause continues, also persists.

We know, from our experience, that heroic doses of quinine do not cure chronic cases. The Indian teaching supports our contention, and analogy with other diseases points the same moral. We have been, in consequence, led to the conclusion that quinine should be given in comparatively short courses, of 3–6 weeks' duration, which may with advantage be repeated from time to time.

But the sheet-anchor in chronic cases is arsenic. It, too, should be given in courses of 3–6 weeks. It may be given by the mouth and pushed to full doses. If it upsets digestion, or fails to produce definite improvement, the next course should be given intravenously. Our results are good and agree with those of others. Its special indication is anaemia, in particular of the pernicious type.

But all drugs are of little value if attention is not paid to those other points to which we have alluded. Of these the most important is rest, and the next protection from the sun and chill. Without attention to these apparent details all treatment is, in our opinion, unlikely to produce rapid or permanent results.

We would emphasize the fact that malaria must not be considered a trifling or a trivial disorder. It is true that it has a small mortality, but it seriously affects the efficiency of our forces. We believe that measures which would admit of energetic and prompt treatment at the outset would prove a valuable investment, and we would urge that neither expense nor temporary expediency should be allowed to interfere with the early treatment of the disease.

It is important to make an accurate diagnosis of malaria at the outset of the disease, before treatment is commenced. This can only be secured by microscopic examination of the blood. If this is omitted the diagnosis is uncertain and can rarely be verified, for the parasites rapidly disappear from the peripheral blood after the administration of quinine. Two courses are then possible: to accept the uncertain diagnosis, or to refuse treatment until the parasites reappear. The latter course may occasion considerable delay, and in the case of a malignant infection be attended by some risk.

At least seven fevers of unknown origin have occurred in the E.E.F. Two are

of short duration, about three days. One is the so-called sand-fly fever, the other is perhaps of gastro-intestinal origin. Two last for about a week. One is probably a mild enterica, though bacteriological tests are negative, while the other is not enterica and may be in some cases Brill's disease. Two are of dengue type. One is true dengue, which is probably rare, while the other is not dengue. The Indian physicians are acquainted with this disease. The seventh type is the form of relapsing fever known in France as trench fever. To these may be added almost every known fever, with but two or three exceptions. The most common are relapsing fever, enterica, typhus, the various P.U.O.'s, and latterly influenza, which, however, did not occur in Egypt until the summer of 1918. The differential diagnosis in the early days of an illness was, in consequence, extremely difficult, and, in the absence of laboratory facilities, almost impossible.

The *mononuclear count* cannot be relied upon for diagnosis. The large mononuclear cells are increased in number in the Palestine form of relapsing fever, in kala-azar, and in some of the undifferentiated fevers of hot climates (Fairley, Rankin, Ferguson and Campbell, Rogers, Warnock). The absence of pigmentation of these cells is also unreliable.

On the other hand, it must be remembered that parasites may not be found in the blood, even in fevered patients, in indubitable cases of malaria. Their presence, or at any rate their recognition, depends largely upon the skill and the pertinacity of the observer. But the presence of parasites at one stage of the illness is an unfailing help in treatment, particularly in those cases which present symptoms of unusual character or marked severity.

It is generally believed that anti-mosquito measures are the most efficacious means of dealing with malaria. But while such measures may be practicable when troops are stationary, they are manifestly impracticable when the force is moving, and the situation dictated by purely military considerations. Even then, however, it may be possible to select camping-grounds so far distant from the breeding-places of mosquitoes that their usual flight is exceeded, or up wind from the breeding-places (Bridges).

When such measures are impossible, mosquito nets and repellents may be utilized. Repellents are, however, only active for a few hours after their application, and a single application does not suffice for all the hours of sleep. But guards and sentries are able to make use of them.

We have already considered the uses of prophylactic quinine in some detail. It seems clear that, *in order to prevent infection*, large doses (probably at least gr. 20 daily) are required. This amount is likely to be injurious to at any rate a proportion of the troops, and in any case cannot be continued for long. Its use would seem desirable in cases where the probability of infection is considerable, but likely to be of short duration (7–14 days).

It also seems clear that smaller doses of quinine, *while not preventing infection*, can prevent the occurrence of malarial attacks, though these not infrequently ensue as soon as the administration of the drug is stopped. This

was frequently noticed among the troops who came to Egypt from Salonika in 1917. In time a tolerance of the drug is induced, so that the dose has to be increased. This tolerance, too, renders the cure of the disease more difficult and prolonged, and necessitates the use of larger doses than are generally required.

The distinction between these measures must be borne in mind. If it is possible, prophylactic quinine should be avoided. If this is not possible, its use should be intermitted whenever the probabilities of infection are slight, so as to lessen the degree of tolerance. If it has to be given continuously the dose has periodically to be increased.

It is inadvisable to use prophylactic quinine in the Royal Air Force, on account of the auditory and visual symptoms which it may produce. Their conditions in camp, however, are usually such that anti-mosquito measures are practicable.

The ideal conditions of treatment of cases of primary malaria are (1) the institution of treatment as soon as the symptoms ensue; (2) the continued administration of quinine in large doses for 3–4 weeks, during which the patient must remain in hospital; and (3) convalescence in a mosquito-free area, preferably at the seaside, or among the hills.

Blood-films must invariably be taken, for future examination, before any quinine is administered, as it is difficult to find the parasites after quinine has been given. The mass of the infection should be gauged, as well as its nature. The absence of parasites does not disprove the existence of malarial infection, but they are rarely absent in cases where fever is present, unless quinine has been administered.

The patient must be kept in bed and at rest during the continuance of the fever, and for some days subsequently. An early resumption of activity is a common cause of failure to overcome the infection.

The diet at first should be fluid and easily digestible. The bowels must be kept open. A mercurial is useful at the outset, and should be repeated twice or thrice weekly.

Quinine should be administered as soon as the diagnosis is made, irrespective of the presence or absence of fever. It is best given in solution, but may be given in powder, in cachets or capsules. Pills and tabloids should not be used, as they are often hard and relatively insoluble. The bihydrochloride, the hydrochloride, and the hydrobromide are the best preparations. The sulphate requires the addition of acid to ensure solution. An aromatic, such as cardamoms or chloroform, should be added to the mixture.

The initial dose lies between gr. 30 and 60 daily. The larger dose is rarely required. The dosage should be gauged by the degree of severity of the symptoms and the mass of the infection as shown on the blood-film (Gill). Gr. 45 is a common dose. It should be continued while the fever lasts, and for 3–7 days subsequently. The dose may then be reduced to gr. 30, and this should

be continued until the patient has been afebrile for at least 21 days. The drug may be given thrice daily after food. Brem recommends that the three doses should be given in quick succession in the morning (cf. p. 10), but we have found that it is generally better tolerated after food. It is sometimes helpful, during the fever, to give it in four-hourly doses. Intolerance of the drug is rare, save in the presence of gastro-intestinal symptoms. Tinnitus and deafness can generally be ignored. They are less troublesome if the hydrobromide is used, or bromide of sodium added to the mixture.

It is essential to make sure that the drug is absorbed. Oral administration is contra-indicated in cases where gastric or intestinal symptoms (vomiting, diarrhoea, dysentery) are present, and in cases where the tongue is thickly furred. Rectal injections are sometimes possible in these cases and the quinine is said to be absorbed rapidly (Fleming). But intramuscular injections are generally necessary. These are also preferable in cases of massive infection as shown on the blood-film, in patients with cerebral symptoms, however slight, or pulmonary or abdominal symptoms, and in cases where the fever is not influenced by oral administration.

There is a general feeling that intramuscular injections are desirable in the early stages of subtertian infections. This is recommended by 9 of 26 officers as a routine, the initial doses varying from gr. 12 to gr. 45. With the smaller doses gr. 20–30 are given in addition by the mouth. One officer recommends intramuscular injections at the outset in benign tertian infections. We believe that there is little difference in the reaction of benign and subtertian infections to quinine, and we are inclined to give some intramuscular doses to all cases at the outset, as we think with Col. MacKenzie that the duration of the fever is shortened.

One officer recommends intravenous injections (gr. 10–15) for the first two days in subtertian infections. This we consider unnecessary. The indications for intravenous injections are those that indicate the necessity for rapid destruction of parasites, i. e. cases with cerebral symptoms of any kind, whether of the comatose or delirious type, and cases with collapse, marked cyanosis, acute abdominal symptoms, or hyperpyrexia.

The bihydrochloride is the most suitable drug for intramuscular injections, dissolved in normal saline solution (gr. 10 in 10 c.c.). It should be injected deeply into the gluteal muscles, well away from the sciatic nerve. The needle should be thoroughly emptied before withdrawal. The most scrupulous asepsis must be maintained.

For intravenous injections, the hydrochloride is most suitable, as the solution is neutral. The usual dose is gr. 10 dissolved in 10 ounces of warm normal saline solution. The injection must be made slowly, 15–20 minutes being occupied in the operation. The maximum daily dose is about gr. 30.

In toxaemic cases the amount of saline solution may be increased to one or two pints. The presence of oedema of the lungs is of course a contra-indication.

The treatment of relapsing malaria differs in some respects from that of primary attacks.

We have classified these patients into three main groups. In one the men are ill, and evidently require hospital treatment. In the second the men are not ill, but are liable to recurring attacks of ague. In the third the men are unfit, but not seriously ill, and are also liable to ague fits.

During attacks of fever all these patients must, of course, be treated in the same way as during primary attacks. One must remember, however, that men who are quinine sodden require much larger doses of quinine than those which would be efficacious in men who are not quinine sodden. Not infrequently the fever persists so long as the drug is given by the mouth, though it passes off at once when it is given intramuscularly. In some cases it persists in spite of quinine.

The reason is not always manifest. In some the alimentary tract is out of order, and success ensues as soon as this is remedied. In some the cause of the fever is not malaria, but some coincident infection, such as enterica, dysentery, or phthisis. A complete examination should always be made in every case, for we have often seen two or three different infections in the same patient—malaria, bacillary dysentery, and ankylostomiasis, for example, or malaria, broncho-pneumonia, and amoebic dysentery. The cause may be an abscess in the buttock, an acute osteomyelitis, a tonsillitis, or a urinary infection. In many cases the real cause is the continuance of the infection, *the patient being too debilitated to overcome the disease*, however much quinine may be given. It is in this group of cases that arsenic is so useful. A. Balfour recommends the addition of a few minims of the liquor to each dose of quinine, a method which is often successful. But we prefer to give it separately. We have tried several methods, all of which are at times useful. A full crescendo course, by the mouth, the dose being rapidly run up to ℥ 30–45 per diem, the whole course lasting for three to four weeks. Liquor arsenicalis given hypodermically in doses of ℥ 3, which Silvester recommends. Or sodium cacylodate, given intramuscularly in doses of gr. $\frac{3}{4}$ for seven days, as suggested by Willmore.

Galyl, kharsivan, &c., are also useful, given by intravenous injection. H. Miller has reported his results in fifty-three cases treated in this way. His cases were carefully chosen from those which failed to react to quinine, and were all debilitated and constantly relapsing. He gave doses of 0·3, 0·4, 0·5, 0·6 grm., at an interval of five days, but he would prefer an interval of a week between the doses. Twelve of these fifty-three cases relapsed within ten weeks, the earliest relapse occurring eighteen days after the cessation of the treatment. The results at first sight do not seem satisfactory, but as all these patients had failed to react to quinine, and were all much improved in their general condition, they are better than the figures suggest.

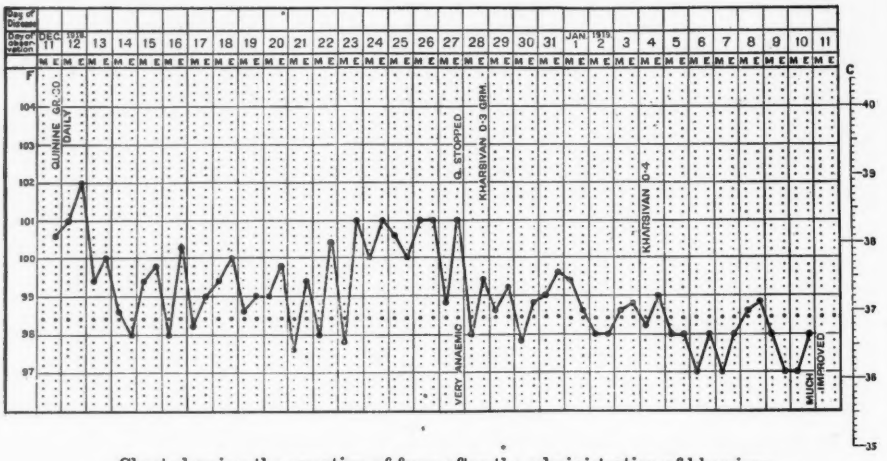

Chart showing the cessation of fever after the administration of kharsivan.

In a general way arsenic is most useful in afebrile cases, but it may be successful in patients who are fevered. The accompanying chart, for which we are indebted to A. K. Hamilton, shows the effect of kharsivan on a patient who had had gr. 30 quinine by the mouth for sixteen days without any appreciable result. The improvement in the man's general condition was striking, and much greater in the week after kharsivan had been started (or after the administration of quinine had been stopped!) than during the preceding sixteen days.

These intravenous injections are most useful in cases of chronic relapsing malaria, with increasing cachexia and loss of flesh, with a hard enlarged spleen, an enlarged liver, and quinine sodden. Albuminuria and cardio-vascular weakness are contra-indications to its use.

Harrington and Whitelaw have used arsenic in these ways with success in another group of cases. They found that a grave form of anaemia, simulating pernicious anaemia very closely in the blood-picture, and only differing from it in the absence of oral and intestinal sepsis, may be the sequel of chronic malaria. It usually, but not invariably, follows subtertian infections. They point out, too, that there is another form of anaemia, of the common secondary type, which reacts well to iron.

It is a common practice to give a course of arsenic and iron, coincidently with quinine, as soon as the fever has gone. This practice is often beneficial, but only in cases which present no gastro-intestinal symptoms. We would draw particular attention to this point. Many patients take quinine, arsenic, and iron without discomfort and with benefit, but others show anorexia, dyspepsia, &c., if such mixed drugging is instituted. In some cases all drugs of these types must be stopped, and a simple alkaline bitter, some pepsin, rhubarb, or nitro-muriatic acid administered, until the *primae viae* are restored to their normal state.

R. H. S. has used intramuscular injections of perchloride (gr. 1/16) of mercury in these cases with benefit. The drug is dissolved in distilled water, and the solution is made up to c.c. 5 with normal saline solution, which neutralizes the slightly acid reaction of the salt. He gives a daily injection for four to five days, and may repeat the course in ten to fourteen days.

In Egypt during 1917 and the early months of 1918 many patients with relapsing malaria were suffering from too much rather than too little quinine. But one must remember that in some patients quinine has never been given a fair trial. The dose has been small and intermittent. Lumb recommends in these cases a two months' course of quinine by the mouth, the daily dose being gr. 20; or a course of intramuscular injections. He gives a first series of twelve injections daily, omitting Sunday, followed by a second series of twelve, given every other day. If a third series is required, the injections are given twice weekly.

In patients who are not seriously ill, groups 2 and 3, a less stringent course is often successful. Gr. 30 may be given for the first week, and gr. 20 for another fortnight (Gill), the course being succeeded by tonics.

Rawnsley's experience in Salonika is of great interest. He had to deal with a heavily infected population, and found, on experiment, that men who were well enough to be serving with their units could take large doses of quinine for a short period with advantage. 38,433 men, of whom 23,071 were known to have had malaria, were consequently given a twenty-four day course of gr. 30 quinine. During the period of treatment 424 men had relapses; during the first month after treatment, 1,695; during the second month, 2,750. In all, 12·66 per cent. of the men relapsed. It was generally believed that, though a complete sterilization had not been effected, the general health had been vastly improved, and many men kept in the line who would otherwise have gone sick. The relapses which occurred were not severe, and readily responded to treatment.

In conclusion, we would again emphasize the importance of estimating, in these relapsing cases, the degree of quinine intoxication, so that one can gauge the dose likely to be efficacious, or suspend the administration of the drug. In other words, *one must treat the patient, and not the disease.*

The treatment of relapsing malaria is not, however, merely a matter of the dosage of quinine. It is essential to improve the general health, and to get the men *fit*. This can rarely be done in hospital. The convalescent homes are useful for a short time after dismissal from hospital, but the command dépôts or special malarial camps are the best places for effecting this end. Each patient must be carefully examined, and his disposal determined by the condition of his general health. It is necessary, in particular, to estimate correctly the amount of exercise that will be beneficial. The only real test is that of experiment. In a general way the course at the command dépôts is too rapid for malarial patients and must be adapted to their capabilities. Malaria is not

a trivial matter. Convalescence takes time. We consider that the average patient who requires to go to hospital is rarely, if ever, fit for the front line under seven weeks, three in hospital and four at the dépôt. It is quite true that robust individuals can sometimes be treated successfully while remaining with their units, but they are the exception and not the rule.

One has, too, to admit that many malarial patients fail to regain their health so long as they remain in the country, and that in that case it is economical to invalid them early to England.

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THE PULMONARY MANIFESTATIONS IN MALARIA

By A. W. FALCONER

THE question whether a pure malarial infection is capable of producing the symptoms and physical signs of bronchitis, pulmonary congestion, and consolidation has been discussed for many years.

Several of the older writers described an intermittent malarial pneumonia in which the symptoms and physical signs were stated to disappear in the apyrexial intervals. Many of the more recent writers regard any pulmonary manifestations which may occur as complications due to a superadded infection, generally with the pneumococcus. Others either ignore the question altogether or are indefinite in their statements. Manson, for instance, states that it is sometimes impossible to differentiate between a malarial and a croupous pneumonia. Castellani states that in many cases broncho-pneumonia in malarial patients is not due directly to the malarial parasite, but is a complication due to the pneumococcus. He, however, recognizes a definite malarial bronchitis, and mentions two cases of malarial consolidation of the lung closely simulating lobar pneumonia. Marchiafava and Bignami state definitely that malaria *per se* is not capable of producing an inflammation of the lung, and they consider that in all cases of 'pneumonia' there is an associated pneumococcal infection. Unfortunately, the term malarial pneumonia has been, by many, very loosely used, and even in some of the more modern papers it seems to mean little more than that in the course of malaria more or less obvious signs may appear in the lungs without evidence of a superadded infection. Marchiafava and Bignami apparently admit that in pneumonic pernicious fever, dyspnoea, cough, bloody expectoration, dullness, bronchial breathing, and fine crepitant râles may appear during the pyrexial periods and disappear in the intervals. These symptoms, they state, are due to congestion of the lungs and a sero-sanguinolent exudation, and, later on, suggest they may be the result of malarial vaso-motor paralysis.

Scheube definitely states that the pneumonic signs represent an expression of the malarial infection itself, and confirms the fact that during the apyrexial stage a remission or complete regression of the subjective and objective symptoms may occur (febris intermittens pneumonica).

Craig states that for a long time pneumonia complicating malaria was held to be due to the malarial plasmodium, and while this is true of a very small number of cases, it should be remembered that true lobar and lobular pneumonia may occur coincidently with any of the malarial fevers.

Crespin and Mailfert, after a full consideration of the subject, conclude that pneumonia is very frequent in the course of malaria; that it is due to the pneumococcus, never to the malaria parasite, although this last may create a certain predisposition by the congestion which it may indirectly provoke in the pulmonary parenchyma. They consider that 'intermittent pneumonia' is a theoretical conception and does not occur clinically, but confirm the fact that, in acute malaria, evidence of consolidation of the lungs may appear and disappear with remarkable rapidity.

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Tsuzuki, in over 500 cases of malaria, found evidence of 'malaria pneumonic' in 8·8 per cent. In over 90 per cent. of these cases the infection was with the malignant parasite. He states that his use of the term 'malaria pneumonic' is to be clearly differentiated from the term 'Intermittens perniciosa pneumonica' of those writers who indicate by this term a condition in which pneumonic signs appear during the malarial paroxysm and are considered by them to represent a pure malarial phenomenon.

He differentiates three groups. I. + Malaria — Pneumonia. In this group the malarial symptoms are in the foreground, and the evidence of pneumonia is only to be found on physical examination of the lungs. The temperature is that of typical malaria, and invariably responds to quinine. The physical signs in his cases were confined to the lower lobes and were generally bilateral. They persisted during the intermissions in the temperature and for some time after its final fall. Ten out of twenty-seven cases showed a certain amount of sputum, and in each case virulent pneumococci were demonstrated in it. He includes 57 per cent. of his cases in this group. He considers that the presence of a complicating pneumococcal infection is proved by: 1. The persistence of the physical signs in the lungs during the intermissions and after the final subsidence of the temperature. 2. 'Das Gefühl völliger Gesundheit' only appears after the disappearance of the physical signs of the lungs. 3. In the sputum, when present, virulent pneumococci were always found.

His second group, — Malaria — Pneumonia, includes five cases, all occurring in the subjects of chronic malaria. The diagnosis of malaria was made by the demonstration of parasites in the blood, and of pneumonia by the discovery of the physical signs of consolidation of the lungs. Symptoms were slight and characteristic neither of malaria nor pneumonia. Two out of the five cases had no fever, and only one had sputum. He considers he is justified in thinking that the pneumococcus was an active agent in those cases on the grounds that the subjective symptoms persisted until the physical signs cleared up, and that a virulent pneumococcus was obtained from the case with sputum.

His third group he designates — Malaria + Pneumonia. These cases are characterized by the dominance of pneumonic symptoms and the inability of quinine to reduce the temperature. In three out of fifteen cases he obtained the pneumococcus from the blood during life. In all cases malarial parasites were demonstrated in the blood.

In all cases, therefore, of malaria with physical signs of consolidation in the lungs Tsuzuki considers that the lung changes are due to a complicating pneumococcal infection, although he points out that in his first group quinine invariably cuts short the temperature, but is ineffective in the third group.

Burgess describes two cases which he considers represent a true 'malarial pneumonia' dependent on the malarial parasite. In the first case, especially, the temperature chart was that of malignant malaria; extensive signs developed at the left base with marked tubular breathing and increased vocal fremitus and resonance. A differential leucocyte count showed 62 per cent. polymorphonuclear cells. There is no note as to the position of the apex beat of the heart. During the apyrexial intervals there was a notable subsidence of the general symptoms, but the physical signs in the lungs remained the same. The sputum showed cocci—probably pneumococci.

Armand-Delille, Paisseau, Abrami, and Lemaire have described the occurrence among the French troops in the Balkans of four pulmonary syndromes which they consider possess sufficiently characteristic clinical features to justify their being attributed to malaria. Their first, and by far the most frequent, syndrome is a mild one characterized by cough, respiratory distress, and the physical signs of bronchitis. The second, — Bronchitis, with pleuro-pulmonary congestion. They emphasize the fact that in this type the symptoms and physical signs are almost entirely pulmonary, and for several days there may be no suspicion of malaria.

The pulmonary signs are characterized by an extreme variability, constantly altering in position and intensity. The patients' symptoms and general condition present the same remissions and exacerbations. The pyrexia is malarial in type.

Their third type, which they state is much rarer, shows all the typical physical signs of an apical pneumonia, including dullness, bronchial breathing, and crepitant râles. The physical signs may relapse *in situ* or in some other part of the lung. Its course runs parallel with the malarial attack and is definitely influenced by quinine. This description corresponds very closely to the apical type previously described by de Brun, and by Crespin and Mailfert.

Their fourth syndrome, which they describe as very rare, is the occurrence of the picture of typical pulmonary apoplexy with often a rapidly fatal termination. Moore had already described this type in 1867.

Captain A. G. Anderson and myself described the physical signs in the lungs observed in a large number of the malarial cases occurring in the British Salonika Force in 1916. We divided them into three groups. I. Bronchitic, which was much the most frequent. II. Pneumonic and broncho-pneumonic, where there was evidence of a superadded pneumococcal infection. III. A group where more or less extensive signs of consolidation appeared without any evidence of a superadded infection.

In the malarial season of 1917 cases of malaria presenting notable pulmonary symptoms were again frequent among the British troops in the Balkans. In 1918, owing to the extreme prevalence of influenza during the acute malarial season, a very large proportion of the cases were suffering from the double infection, and the interpretation of any lung symptoms which they might present was rendered more difficult and any attempt to estimate the percentage frequency of lung symptoms in malaria impossible.

The pulmonary manifestations which were observed can be classified into the following groups:

I. Bronchitic. II. Pleuro-pulmonary congestion with more or less definite evidence of consolidation. III. Massive collapse of the lung. IV. Concurrent malaria and pneumonia. V. Pneumonia occurring in chronic malaria without evidence of active malaria. VI. Pleurisy, either dry or with serous or haemorrhagic effusion.

I. Bronchitic. This type represents by far the most common pulmonary manifestation in malaria. A large number of the cases were sent into hospital with a diagnosis of bronchitis. The patients complained of cough, dyspnoea, and pain in the chest. On examination, the chest presented the usual features of bronchitis, with the presence of numerous rhonchi and râles throughout the lungs. A characteristic feature of the stethoscopic signs was the notable way in which they varied within a few hours and flitted about from one portion of the lung to the other. If the case was associated with an intermittent pyrexia, both the symptoms and physical signs were notably aggravated during the pyrexial periods, and diminished, but generally did not completely disappear, in the apyrexial intervals. The sputum was generally profuse and fairly characteristic. It was a thick, uniform, almost pure white homogeneous sputum of cream-like

consistency. The temperature chart might show a typical malarial intermittent fever, an irregular intermittent pyrexia, or a normal or subnormal temperature. As a rule, malarial parasites were readily demonstrated in the blood, and were either the benign or malignant tertian variety.

Untreated with quinine, the physical signs in the lungs persist for days, or, in certain cases, become more marked and altered in character. When adequately treated with quinine the rapidity with which they disappear is dramatic. Notable signs which have been present for several days will often completely disappear within twenty-four hours.

In a certain proportion of these cases a superadded infection is possible, and in unrecognized and untreated cases is extremely liable to supervene; but from the somewhat peculiar character of the physical signs, and more especially from their dramatic response, in the great majority of the cases, to adequate quinine treatment, I think one is justified in concluding that the physical signs are the direct result of the malarial process. It is difficult to understand how such an immediate and complete recovery could occur in the presence of an active superadded infection.

II. Pleuro-pulmonary congestion with more or less definite evidence of consolidation. Cases of this type were not uncommon. In the more marked instances they corresponded to the cases of apical consolidation described by de Brun and Crespin and Mailfert and to the third group of Armand-Delille, Paisseau, Abrami, and Lemaire. The signs are not, however, limited to the upper lobes, but may appear in any part of the lung. Clinically they are characterized by the appearance of definite evidence of consolidation, slight dullness in percussion, bronchial breathing, and crepitant râles, without any of the general symptoms of pneumonia. As pointed out by Crespin and Mailfert and others, a characteristic feature of the physical signs is the rapidity with which they may vary. Definite evidence of consolidation may be present at an apex or base one day and gone the next, possibly to appear in some other part of the lung. In other cases the signs persist for several days. In many cases the general symptoms are extremely slight. Many of the patients do not appear ill, especially in the apyrexial intervals. In other cases the general condition is grave apart from the lung condition. Cough and expectoration are generally present, but expectoration may be absent. When sputum is present it is frequently similar to the dead white homogeneous sputum of the bronchitic cases. In some cases individual masses of the sputum may be bloodstained, and occasionally free haemoptysis is seen. The sputum has not the typical tenacious rusty character of pneumonic sputum, although pneumococci and other organisms may be present on microscopical examination. The temperature chart shows one of the types of malarial temperature and bears no clear relationship to the extent of the physical signs in the lungs. Fresh areas of apparent consolidation may appear without any rise of temperature or aggravation of the general symptoms. Respiratory distress, if present, is, however, nearly always more marked during the pyrexial

period, to notably diminish or disappear in the apyrexial interval. The blood shows no leucocytosis, and, unless quinine has been administered, malarial parasites are generally readily demonstrated in the blood. Adequate quinine treatment has a very definite effect on the condition, and the majority of the cases do well.

I have had an opportunity of examining only two cases post mortem.

Case I. Male, aged 42, had reported sick a week before admission to hospital on account of a rigor followed by sweating and accompanied by pain in the limbs. He had been taking quinine in small doses from that date. On admission to hospital his general condition was fair, his temperature was normal, and he had no respiratory symptoms. On examination it was found that there was impairment of resonance at the base of the right lung, with bronchial breathing and increased vocal resonance. There was no cough or expectoration. His temperature remained below 99° F. for three days, when he suddenly developed a pontine paralysis and died within 12 hours. At the autopsy, in addition to malarial changes in the pons, the lower third of the lower lobe of the right lung was found collapsed. Sections of the lung showed intense congestion of the capillaries, producing a notable thickening of the alveolar wall. In part this was associated with collapse of the alveolus and in parts of small haemorrhagic infarcts. Malarial parasites were present in small numbers. There was no inflammatory consolidation.

Case II. Pte. D., aged 42, admitted to hospital from a malarial convalescent dépôt. On admission his temperature was 99° F. There was some impairment of the percussion note at the base of the right lung. I saw him next morning. His temperature had risen to 103° F., respirations 48, pulse 112. He was in an extremely collapsed condition, with incontinence of urine and faeces. There was considerable dyspnoea and some cyanosis. Examination was difficult on account of his condition, but he had numerous rhonchi and râles over both sides of his chest in front and distinct impairment of the percussion note over the right base behind, with tubular breathing and increased vocal resonance. The leucocyte count showed total leucocytes 6,000 per c.c.; polymorphs, 48·5 per cent.; small lymphocytes, 6 per cent.; large lymphocytes, 42·5 per cent.; mast cells, 3 per cent. The blood-film showed numerous malignant tertian parasites. He was given pituitirin and 30 grains of quinine bihydrochloride intravenously in one pint of saline. Next morning patient's general condition was much improved. His temperature was 98° F., pulse 88, respirations 26 a minute. He had practically no dyspnoea, but his lungs were not examined on account of his condition. He received 30 grains of quinine intramuscularly in the morning, and as parasites were still present in large numbers in the blood at 4 p.m. he received another 30 grains of quinine intramuscularly. At 6 p.m. he was quietly asleep, but was found dead in bed at 7 p.m. Colonel Dudgeon, C.M.G., Consulting Bacteriologist, B.S.F., reported that the base of the right lung showed extreme congestion of the capillaries in the alveolar walls, giving rise to apparent consolidation, some pulmonary collapse, parasites numerous, no inflammatory consolidation.

It will be noted that, on the day after admission, with the fall in the temperature the pulmonary symptoms were much relieved, the respirations fell from 48 to 26 a minute, and the patient apparently was quite comfortable. Blood examination, however, still showed a heavy infection, and, as not infrequently happens in malignant malaria, the patient suddenly died of cardiac syncope.

As further examples of extensive signs of apparent consolidation in the lungs without the general signs of pneumonia the two following cases may be quoted. In both malignant tertian parasites were demonstrated in the blood.

Case III. Pte. F., aged 20. Reported sick on October 22, complaning of shivering, malaise, and diarrhoea. He was admitted to hospital on the 29th. On admission he was pale with a slight icteric tinge of the sclerotics. The spleen extended to three fingers' breadth below the costal margin. Anteriorly over the left lung there was bronchial breathing over the 2nd, 3rd, and 4th intercostal spaces. There was no definite dullness in percussion and the vocal fremitus and resonance were not markedly increased. Behind, over the left lower lobe, there was bronchial breathing, with numerous medium-sized moist râles. The physical signs persisted for ten days. On the day of admission to hospital the temperature rose to 103° F. Next day it did not rise above 99° F., but on the following day rose to 103° F. Thereafter it did not rise above normal. There was little cough and no expectoration. He was treated with intramuscular quinine.

Case IV. Male, aged 29. Reported sick on November 1, complaining of pain in the chest, shortness of breath, and headache, and was admitted to hospital on November 4 with a diagnosis of congestion of the lungs. He did not look ill, and had none of the general appearance of pneumonia. Dyspnoea was evident only on exertion. The spleen was palpable. Anteriorly over the right lung, both above and below the clavicle, the breath sounds were bronchial with numerous moist sticky râles. Posteriorly the percussion note was impaired in the right supraspinous fossa and at the right base. In the supraspinous fossa the breath sounds were bronchial in character, and over a small area just below the spine of the scapula they were distinctly tubular. Numerous râles were present all over the right lung and a few at the left base. On admission to hospital the temperature was 99·8° F. On the following day the temperature again rose to 99·8° F., but thereafter remained normal. The physical signs in the right lung gradually cleared up, but on November 12, without any rise of temperature or increase in the patient's symptoms, a large area of apparent consolidation suddenly appeared in the left lower lobe, accompanied by numerous moist râles. This also slowly cleared up under quinine treatment.

III. Massive collapse of the lung.

This appears to be a not very uncommon occurrence in malaria, but is generally overlooked or described as pneumonia. It is quite possible that in many of the cases included in Group II the physical signs depend not on consolidation but on partial collapse. Massive collapse may affect either the upper or lower lobes, but in my experience is most frequent in the left lower lobe. The method of production is obscure. In certain cases it may be due to the blocking of a bronchus by secretion; in others, especially when the collapse affects the left lower lobe, it may depend on impaired movement of the diaphragm, possibly dependent on perisplenitis. The collapse may rapidly pass off or may persist for several weeks.

The following cases are examples of massive collapse of the lung occurring in malaria:

Case V. For the notes of this case I am indebted to Dr. B. M. Cunningham.

Pte. C., aged 28, was admitted to hospital with a history of rigor, vomiting, and pains in the limbs. Six weeks previously he had had an attack of malaria. On admission to hospital there were a few rhonchi in the lungs. He was put on 30 grains of quinine sulphate daily by mouth. On the 21st he developed diarrhoea with blood and mucus in the stool, and a Shiga bacillus was recovered from the stool. He was at once given antidysenteric serum and the diarrhoea completely subsided in two days. On the 24th the bowels moved once and there

was no blood or mucus in the stool. On the morning of the 24th the patient complained of some pain behind the sternum and the lungs presented a few scattered rhonchi. The apex beat of the heart was noted half an inch inside the nipple-line. At 4 p.m. on that date Dr. Cunningham was called to see the patient. He was complaining of severe pain in the chest, which was so severe that he was weeping. The pain was referred to the sixth left costal space and radiated across the left mamma. The respirations were 36 per minute and were accompanied by a grunt at the end of expiration. The pulse was small, regular, and its rate was 96 a minute. The apex beat of the heart was very visible, tumultuous, and was situated in the fourth costal space one and a half inches outside the nipple-line. There were no murmurs. The lungs showed sibilant rhonchi over both lungs anteriorly, most marked on the right side. The back of the chest was not examined as the patient was too distressed. A blood-film taken at the time was negative to malaria, but the patient had been on 30 grains of quinine sulphate daily for some ten days. At 7.30 p.m. the patient was easier and the pain had almost gone. On the 25th the temperature rose to 101° F. The apex beat of the heart was now in the fourth space, one inch external to the nipple-line. Anteriorly the lungs still showed numerous rhonchi over both sides of the chest. There was a copious sputum consisting of thick dull white fungoid-like masses. He was given 20 grains quinine bihydrochloride intramuscularly and 30 grains of quinine sulphate continued daily by mouth. I saw him on the morning of the 26th. He was by then much easier. The temperature was 99° F., respiration 24, and pulse 90 per minute. The apex beat of the heart was in the fourth interspace, half an inch external to the nipple-line. The lungs showed distinct flattening and narrowing of the intercostal spaces in the left axilla. In the left axilla and at the left base from the spine of the scapula downwards, the percussion note was notably flat but not absolutely dull. On auscultation over this area the breath sounds were tubular, in parts almost amphoric, and there was extremely well-marked whispering pectoriloquy. Over the right lung the breathing was harsh and compensatory with scattered rhonchi. The sputum was profuse and consisted of dull white masses. Microscopically it was mainly polymorphonuclear and contained pneumococci, some of which were within the polymorphs. Unfortunately a skiagram of the chest could not be obtained. The quinine was continued by mouth and he was ordered ten grains of quinine daily intramuscularly in addition. On the 27th the patient was perfectly comfortable, the sputum had almost ceased. The apex beat of the heart was still a quarter of an inch outside the nipple-line. The expansion of the left base was much improved, but there was still tubular breathing and whispering pectoriloquy at the extreme base. On the 28th he was free from symptoms, the sputum had quite ceased. The apex beat of the heart was in the fourth space half an inch inside the nipple-line. The percussion note at the extreme left base was slightly less resonant than on the right side and there was slight impairment of air entry, but otherwise nothing abnormal could be made out. From this date onwards he presented no further symptoms.

Although the sputum in this case did contain pneumoccoci, the physical signs were those of massive collapse and not of consolidation. The patient's distress came on absolutely suddenly, was very marked for a few hours, and then became much less and was practically gone in twenty-four hours. There was no leucocytosis. The temperature was only raised for some twenty-four hours. In view of these facts it seems impossible to regard the collapse as a result of a pneumococcal infection, but it does indicate how readily such a secondary infection may occur.

Case VI. Cpl. S., aged 20. Readmitted to hospital from a malarial convalescent dépôt. On admission to hospital the temperature was 104·8° F., pulse 104, respirations 36 per minute. A blood-film showed numerous malarial rings of uncertain type. A few crepitations were found over the right

scapula. He was put on thirty grains of quinine sulphate daily by mouth. From September 23 to October 1 he showed an irregular intermittent fever. On September 24 he suddenly began to expectorate freely. The sputum consisted of dull white homogeneous masses. On the 25th the sputum continued and he had slight haemoptysis. On the 26th his temperature was normal and he was much more comfortable. The sputum had almost ceased. On the 28th the temperature again rose to 100° F. and coarse râles were heard over the front of the right chest. The sputum again increased. I saw him on October 1. His temperature was 97° F., pulse 68, respirations 24 per minute. He was perfectly comfortable, but was expectorating freely. On inspection of the chest the right side was notably flatter than the left and the intercostal spaces narrower. The apex beat of the heart was in the fourth space, one and a half inches inside the nipple-line. The percussion note on the right side in front down to the fourth rib was very definitely dull but not absolutely flat. On auscultation over this area the breathing was tubular with well-marked whispering pectoriloquy. There were no adventitious sounds. Behind, at the right base, the breath sounds were diminished but not otherwise abnormal. A skiagram obtained on this date shows very definite narrowing of the intercostal spaces over the right upper lobe, marked increased opacity of the right upper lobe, and very definite displacement of the heart to the right. From this date onwards the temperature remained normal and the physical signs in the right lung rapidly cleared up. On the 5th of October the apex beat of the heart was just inside the nipple-line.

Case VII. Pte. M., aged 24, admitted to base hospital on 9.7.17. His illness had started on 30.6.17 with a rigor, followed by sweating, headache, and pains in the back and the chest. On the 4th of July he developed a cough but no expectoration. On admission to hospital his temperature was 98° F., pulse 120, respirations 24 per minute. Examination showed defective movement of the whole of the left side of the chest with dullness on percussion, tubular breathing, and marked increase in the vocal resonance at the left base. The position of the apex beat of the heart was not noted. His physical signs remained *in statu quo* and his temperature normal until July 15, when he had another rigor and his temperature rose to 104° F. Malignant tertian parasites were found in the blood and he was then put on quinine treatment. On July 16 his temperature again rose to 102° F., but fell to normal on the morning of the 17th, and, except for a rise to 100° F. on the 20th, remained normal for the rest of his stay in hospital. On the 22nd he was allowed up, although the physical signs in the lungs had remained stationary. I first saw him on August 10. His general condition was excellent, and he was walking about the ward without discomfort. On examination of the chest there was marked shrinking and limitation of movement at the left base. The intercostal spaces were notably narrower than on the right side. The apex beat of the heart was situated three-quarters of an inch outside and just below the nipple-line. From the lower angle of the left scapula downwards the percussion note was almost dead dull. On auscultation over this area the breathing was tubular, almost amphoric, with very well-marked whispering pectoriloquy. There were no adventitious sounds except a slight pleural friction rub. An X-ray obtained on this date was reported on as follows:

'On the right side there is considerable mottling of the whole lung and peribronchial thickening at the root of the lung. The left lung casts a much denser shadow than the right, and this, with the displacement of the heart to the left and the falling together of the ribs, suggests collapse of the lung.'

His general condition remained excellent and he had no complaints. An X-ray examination on 29.9.17 was stated to show far less collapse of the thoracic wall than the previous examination and that the central area of the lung now hardly differed from that of the opposite side, although the base still showed increased density. Physical examination still showed the apex beat situated just outside

the nipple-line and an area of tubular breathing with whispering pectoriloquy at the extreme base. He was evacuated to hospital ship in this condition.

IV. Concurrent malaria and pneumonia.

All observers are agreed that this is not an uncommon event in malaria, and the pneumococcus has been frequently recovered from the blood in such cases. Clinically, however, these cases differ in certain important respects from the cases already considered. The patients, in addition to any malarial features which they may present, show more or less definitely the general features of pneumonia. The temperature is much more a continuous temperature, the physical signs are those of consolidation, and they do not show the rapid variations in site and character which is so characteristic of some of the former groups. If remissions do occur in the temperature there is not the same symptomatic improvement. The sputum is generally that of typical pneumonia. The blood frequently, if not always, shows a definite polymorphonuclear leucocytosis, and the pneumococcus may be obtained from the blood. Malarial parasites may be present in the blood, but often apparently tend to disappear when the lung symptoms appear, even apart from any treatment by quinine. Once the lung symptoms are definite quinine treatment has apparently no influence on the condition.

The following two cases are examples of pneumonia complicating malaria:

Case VIII. Pte. S., aged 21, admitted to hospital on 4.11.17. Reported sick on 2.11.17, complaining of rigor, headache, and pain in right chest on deep breathing. He had had two previous attacks of malaria. On admission to hospital his temperature was 104·6° F., pulse 88, respirations 36 per minute. He had a short frequent cough with typical tenacious, rusty sputum. There was dullness to percussion at the right base, with tubular breathing and increased vocal resonance. The rest of the lungs showed no abnormal signs. The apex beat of the heart was in the fifth space in the nipple-line. For the first two days he was treated with intramuscular and intravenous quinine without effect. His temperature remained constantly high until 10.11.17, when it began to subside by lysis, reaching normal on 14.11.17. The physical signs slowly cleared up and were quite gone by 8.12.17. Three blood-films were negative to malaria at the height of the fever, but on 2.12.17 patient had a rigor and the temperature shot up to 105·2° F. Benign tertian parasites were then found in the blood. Total leucocyte counts made on 8.11.17 and 13.11.17 showed a leucocytosis of 11,000 and 17,000 respectively.

Case IX. Pte. H. admitted to hospital on 9.11.17. He reported sick on 6.11.17, complaining of headache and pain in the right side of the chest. He had had malaria in August 1916 and nine or ten relapses since. On admission to hospital his temperature was 104·6° F., pulse 120, respirations 30 per minute. His general condition was bad, his spleen was readily palpable, his conjunctivae icteric. The percussion note below the angle of the right scapula was dull and the breath sounds bronchial, with increased vocal fremitus. The rest of the lungs were clear. The sputum was typically tenacious, rusty sputum. The apex beat of the heart was in the fifth space in the nipple-line. Malarial parasites were not found in the blood. On the 12th there was a leucocytosis of 15,600. For two days he was treated energetically with quinine without improvement. The temperature continued high until the 14th, when it fell by rapid lysis and the physical signs in the right lobe slowly cleared up.

V. Pneumonia occurring in the course of chronic malaria without evidence of active malaria.

These cases differ very little from those in the preceding group and are chiefly of importance from the point of view of treatment. If active malaria is present it is advisable to push quinine for the first day or two, to overcome the malarial infection. If not, this is unnecessary. The absence of parasites from the peripheral blood, especially in the presence of pneumonic symptoms, does not, however, justify one in assuming that the malaria is quiescent, and the differentiation must be made from the absence of other features suggesting active malaria.

VI. Dry pleurisy, or pleurisy with serous or haemorrhagic effusion.

The occurrence of pleural friction rub is not uncommon in cases where there is no evidence of a superadded infection. Rarely a serous effusion follows in the course of malaria, and on three occasions I have explored and found a deeply-stained haemorrhagic effusion, which in all cases was sterile.

Conclusions. That although malaria is frequently complicated by pneumococcal infection, numerous cases occur in which there are notable changes in the lungs without any evidence of superadded infection. These may present the physical signs of bronchitis, pulmonary congestion with more or less definite evidence of consolidation, or massive collapse of the lung. In many cases the symptoms at first are almost entirely pulmonary and the malaria infection may be entirely overlooked. Its recognition at the earliest possible moment is important, as untreated with quinine there is a great liability for the lung to become secondarily infected with the development of true inflammatory changes.

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OBSERVATIONS ON RESPIRATION AND CIRCULATION IN THE GOAT

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1. THE quantity which is fundamental in almost all of the problems connected with the efficiency of the circulation is the amount of blood which passes through the lungs in unit time, or, as it is conveniently called, the 'minute volume'. A variety of difficulties have obstructed the full examination of the minute volume, taking in some cases the form of technical experimental obstacles, in others methods of theoretical uncertainties. In the following paper a method is described by which the minute volume can be determined with comparative ease and with apparent precision.

2. The *animal* used must be large, so that (1) the repeated extraction of 5 or 10 c.c. of blood shall be as nearly immaterial as possible, and (2) the heart-wall shall be thick and extensive enough to withstand repeated punctures with a hollow needle. As the experiments have to be made on unanaesthetized animals, it is desirable also to use a sort of low emotional excitability. We have found the goat very suitable; it is comfortably sized, and, as a rule, wonderfully passive under experiment. Some goats, however, resent being handled at first, and are inclined to struggle when on the table.

The principle of the method is due to Zuntz, and is as follows:

If O be the total oxygen in c.c. used by the animal per minute, A the c.c. of oxygen in 1 c.c. of arterial blood, V the c.c. of oxygen in 1 c.c. of venous blood, and F the c.c. of blood flowing through the lungs per minute, then $F = \frac{O}{A-V}$.

Putting on one side as now discredited the view held by Bohr (1), that a substantial amount of the oxygen disappearing from the expired air might be used by the lungs themselves, the theory of the method seems to be unimpeachable. This cannot, however, be said so confidently of some of the experimental details.

In practice the method as used by Zuntz (2) has been modified so that estimations can be made on the same animal from time to time, and thus records obtained of the minute volume over a period of days or weeks. For this purpose only small quantities of blood must be used for analysis, and not, as in Zuntz's experiments, the amounts demanded by a blood-gas pump. Moreover, nothing in the nature of a surgical operation is admissible, hence Zuntz's technique for obtaining

the blood, which consisted in (1) passing a tube through the jugular vein into the heart, and (2) putting a cannula into an artery, is impossible.

3. *Blood samples* are obtained directly from the heart with a hypodermic syringe—the method of cardiac puncture being used in pathology for other purposes. One of the problems which has for long occupied the attention of blood-gas workers is that of obtaining a fair sample of the gases in arterial blood. The use of anaesthetized animals for this purpose is open to the objection that the

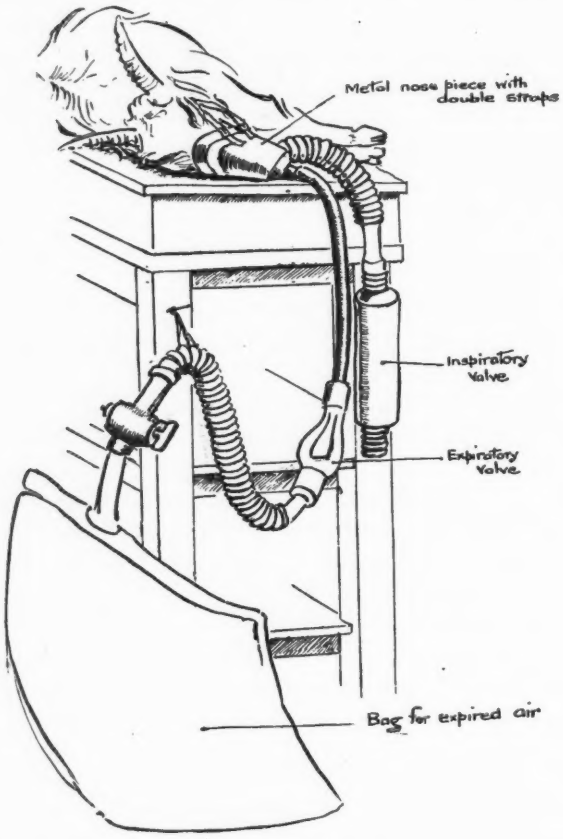

FIG. 1.

anaesthetic may upset the circulation, the respiration, and the secretory activity of the lung if such exists. As regards venous blood, it is well known that the blood from different veins differs greatly in composition. The classical example of this difference is to be found at the confluence of the vena cava and the renal veins, the black flow from the legs forming a striking contrast to the red blood from the kidneys; the difference in colour is so marked as to be seen plainly through the wall of the venae in rabbits. Evidently, therefore, the average venous blood of the body must be drawn from the heart, and just samples of

arterial and venous bloods may be obtained with ease and rapidity in the goat by direct puncture of the heart through the skin and body-wall with a hypodermic needle to which a syringe is fitted. The process, moreover, may be repeated an almost indefinite number of times without apparent injury, and with but little inconvenience to the animal. The main sources of trouble, if any, are pneumothorax caused by puncture of the lung, should this cover the right heart, and haemopericardium. The latter appears to be liable to occur only where the animal is making violent respiratory efforts and the heart is being moved rapidly backwards and forwards by the movements of the diaphragm. The haemorrhage is derived from branches of coronary vessels which have been lacerated by the needle and not apparently from leakage through the ventricular walls. It is rarely fatal in amount, but the possible influence of even a small amount of blood in the pericardium on the efficiency of the heart has to be borne in mind.

4. *Technique of heart-puncture.* It has been found most convenient to perform the punctures with the animal lying on its right side. Both ventricles can be reached from the left side of the chest with the animal in this position. The syringes we have used have been well-fitting 5 c.c. 'Record' syringes; the needles should be $1\frac{3}{4}$–2 inches long. The dead space in the needle is filled with 10 per cent. sodium citrate.

(*a*) The *left ventricle* should be attacked first. With a goat of average size—say, 20 to 25 kilos—it is reached through the fourth intercostal space at a point about three finger-breadths from the ventral aspect of the sternum, at which point the heart is usually to be felt pulsating strongly. The needle should be thrust in almost vertically for a distance of about half an inch, when the point may be felt to scrape on the surface of the heart. A quick thrust of three-quarters of an inch should then bring the point well inside the ventricle. In many instances a successful puncture is immediately followed by the ascent of blood into the syringe. Failure to obtain blood is most probably due to the needle-point being embedded in the septum, in which case success may be obtained by puncturing again from the same spot with the needle-point slightly inclined towards the tail. In the larger animals the heart is usually lower in the thorax, i.e. nearer the tail, while in smaller ones it is frequently higher, i.e. nearer the first rib. In each case the puncture is made in the fourth space, but the needle-point is directed under the fifth rib in the larger, and under the fourth rib in smaller beasts.

(*β*) The *right ventricle* lies mainly in front (i.e. in the direction of the first rib) of the left and somewhat to the animal's right side. It may be reached, as a rule, from the third left intercostal space at a point two to three finger-breadths from the ventral aspect of the sternum. In an average-sized goat the heart would be felt as described above, the needle being directed vertically. In animals of smaller or larger size an indication of the position of the right ventricle will have been obtained from the puncture of the left ventricle. Apart from the colour of the blood, a correct idea of which ventricle has been tapped may be got

by detaching the syringe from the needle and observing if the blood is ejected forcibly or not: this may be done after the syringeful has been taken.

5. *Measurement of blood-gases.* With the samples so obtained it is required to ascertain the quantities of oxygen in 1 c.c. of arterial and venous blood respectively. The difference between the two may be measured directly in the differential blood-gas apparatus (3).

6. The *concentration of haemoglobin* in terms of oxygen capacity is determined either by ferricyanide in the blood-gas apparatus or with the Haldane haemoglobinometer—in actual practice by both methods.

The following table gives a comparison of the haemoglobin determinations by two methods of the blood of two normal goats over a period of three days each:

Date.	Time.	Haemoglobin by Haldane's method.	Haemoglobin by ferricyanide.
Goat 4,444.			
26.8.18	11.15 a.m.	53	—
,,	6.45 p.m.	46	47
27.8.18	12 noon	—	51
,,	7 p.m.	50	50
28.8.18	11.45 a.m.	54	57 55
,,	5.35 p.m.	51 56 54	53
Goat 4,648.			
27.8.18	11 a.m.	65	67
,,	5.45 p.m.	67	69 70
28.8.18	1.15 p.m.	64	61
,,	6.45 p.m.	62	—
29.8.18	10 a.m.	61	57 61

There seems to be no disparity in the figures furnished by the two methods other than is attributable to the errors of reading the apparatus; the greatest difference observed being 4 per cent. The average of the readings for goat 4,444 is 52 per cent. by both methods, and that of 4,648 is 64 per cent. by both methods. In taking this average of the figures for the purpose of calculating the errors it is not suggested that the haemoglobin value remained constant from time to time.

7. *Measurement of respiratory exchange.* The apparatus for this purpose is shown in Fig. 1. The goat wears a metal mask fitting tightly on to its face, with an inflated pneumatic cushion round the edge. Inspiratory and expiratory rubber valves are inserted at appropriate places in the circuit. The expired air is collected in a Douglas bag, measured in a gas-meter, and analysed in a Haldane apparatus. Some dead space in the mask cannot be well avoided; for the present purpose it is perhaps not very material, but if it is desired to take it into consideration something between 50 and 100 c.c. may be allowed for the total dead space.

8. *Sources of error.* In this simple procedure there are a number of small ways in which errors may be introduced.

(*a*) As regards the *animal*, struggling is the chief difficulty. Some idea of the degree of increased metabolism due to this may be obtained from the gas exchange, but violent irregular muscular movements are known to have a considerable influence on the venous circulation, and this cannot be evaluated. Experiments, therefore, in which substantial struggling occurs must be rejected, and the first observation on a fresh animal is rather often of this sort.

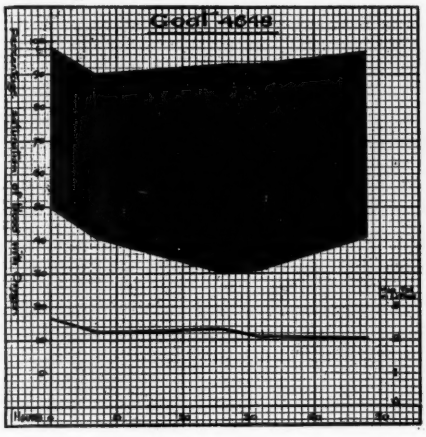

FIG. 2.

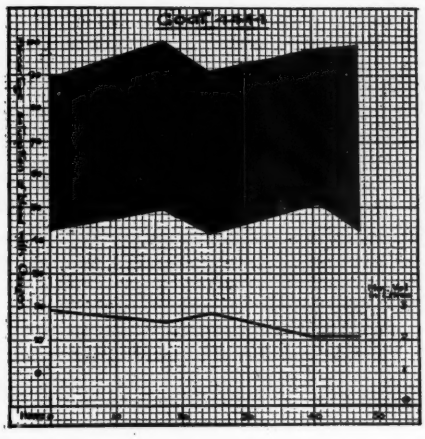

FIG. 3.

Top edge of black area = percentage saturation of arterial blood. Lower edge = percentage saturation of venous blood. Black line, referred to scale on right-hand side = minute volume.

(*β*) The *time relations of the measurements* are not ideal. The arterial and venous samples are never strictly simultaneous; with the best of luck and dexterity they are separated by about thirty seconds, and with ill fortune by perhaps two or three minutes. The measurement of the respiratory exchange cannot be made very well with a period of observation of less than about three minutes, and five minutes may be necessary with a small goat or with very quiet respiration.

(*γ*) *In the analysis of the blood-gases*, the principal sources of error to be guarded against in the method are sedimentation in the syringe and inaccurate measurement of the quantity of blood for analysis. If there is a considerable difference in the composition between arterial and venous blood the method should be almost as accurate as is the measurement of the quantity of blood used; and the difference observed should be within about 5 per cent. of the correct value—duplicate samples differing at most from one another by 10 per cent. It has been our habit to take duplicate analyses, and those obtained from goats 4,444 and 4,648 may serve as samples.

Difference between Arterial and Venous Blood in c.c.

Date	26.8.18.	26.8.18.	27.8.18.	27.8.18.	28.8.18.	28.8.18.	29.8.18.
Hour	Morn.	Aft.	Morn.	Aft.	Morn.	Aft.	Morn.
Goat 4,444	0·051 0·046	0·040	0·051 0·056	0·043	0·048 0·049	0·054 0·056	—
Goat 4,648	—	—	0·061 0·059	0·063	0·075 0·069	0·066 0·066	0·062

The agreement of the duplicates with one another, and the agreements of the ferricyanide readings with those of the Haldane haemoglobinometer, made us feel considerable confidence in the accuracy of the blood-gas measurements.

(*δ*) The measurement of the *oxygen consumed* is liable to a number of corrections. The volume breathed has been measured at the prevailing temperature and pressure in a dry gas-meter; ordinary variations in these could not well make an error of more than 0·1 litre in the minute volume. A mistake of 0·1 per cent. in the determination of the oxygen in the expired air would introduce an error of like magnitude (i. e. less than 5 per cent). The respiratory quotients observed vary widely, likely enough owing to the goats belching up gas rich in CO_2 from their stomachs, and the conversion of these to the actual quotients by calculation from the percentage of nitrogen (3) found makes a substantial difference in the answer in many cases; all the figures have therefore been corrected for this. The belching habit renders the CO_2 figures less reliable. This, however, is not the only source of error in the determination of the minute volume as based on the oxygen rather than on the carbonic acid measurements, and especially if the conditions involve exercise. Muscular contraction frequently causes the formation of lactic acid, a circumstance which secondarily affects the carbonic output—our experience being the same as that of Zuntz, who found that estimations based on the carbonic acid figures did not agree with those based on the oxygen figures, and of the two there can be no doubt that the oxygen data are the ones to accept.

(*ε*) Taking a general view of all these possible errors, we should conclude that the answer in an experiment which has seemed to go smoothly is right to less than 10 per cent., possibly to 5 per cent., some of the errors being proportional, others absolute. The uniformity—or lack of it—found in successive observations on the same animal is illustrated by goats 4,444 and 4,648 (see Table I): the extreme variation from the mean is less than 20 per cent. in each case. Obvious refinements of the method are possible: how far they would be efficacious in securing greater regularity is rather doubtful as long as the general activity of the experimental animal remains so much beyond control.

Some of the data obtained from goats 4,444 and 4,648 are shown in Figs. 2 and 3 respectively. In each case the upper margin of the black area shows the percentage saturation of the arterial blood. The lower margin shows the percentage saturation of the venous blood, whilst the line shows the amount of blood which traverses the thorax per minute.

9. The results obtained in normal goats are set out in Table I, which gives the data for forty-three experiments on twenty-one goats; in Table II these are summarized so as to give one figure for each animal and so facilitate the comparison of one goat with another on data of unequal value.

The sort of uniformity which is obtained in successive experiments on the same animal is illustrated by 4,444 and 4,648. The same two animals show the individuality which renders it impossible to assume any average normal value of practical utility; the constants for each animal must be ascertained before it is subjected to pathological experimental procedures. Thus, throughout, 4,648 breathed slower and worked at a higher CO_2 pressure than 4,444, the total consumption of oxygen being about the same absolutely, but considerably higher per unit body-weight for 4,648; the oxygen difference between arterial and venous blood is persistently lower in 4,444, and consequently the volume of blood circulated for each c.c. of oxygen consumed is regularly higher. An animal of singular habits is 5,122: the exceptionally low oxygen consumption and correspondingly sluggish circulation would make us very suspicious of some substantial error were they not confirmed by three concordant experiments.

The mean figures for the various values speak for themselves. No definite influence of weight or sex can be made out for this particular series of animals.

Some consideration has been given to the relations of the various factors measured to one another, such, for instance, as that of the oxygen consumed to the oxygen difference observed in different animals, but no general principle has been forthcoming. That being so with regard to measurements which are in no way dependent upon one another, there seems at present to be no object in extending the inquiry to factors which are not independent variables, such, for instance, as the minute volume and the oxygen difference in normal animals. These subjects, however, might form the basis of future experiments.

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TABLE I.

Goat No.	Body Weight.	Date.	Respirations per min.	Expired Air, litres per min.	Expired Air, c.c. per kg. per min.	C.c. per Breath.	% CO_2 in Expired Air.	% O_2 in Expired Air.	Total CO_2 per min., c.c.	Total O_2 per min., c.c.	CO_2 per kg. per hour.	O_2 per kg. per hour.	R.Q. (corrected).	% Saturation, Arterial Blood.	% Saturation, Venous Blood.	Hb % on Human Scale.	Minute Volume, litres.	Min. Vol., c.c. per kg.	Min. Vol., c.c. per c.c. O_2 used.	O_2 difference, c.c. O_2 per c.c. blood.
3632	38·6 kg.	11.6.18 2.50 p.m.	17	8·42	218	496	2·86	17·57	238	295	370	458	0·81	95·5	58	78	5·60	145	19	0·0525
3456	38·4	10.6.18	15	9·51	304	633	2·93	17·53	276	329	528	628	0·84	97	30	86	3·82	121	12	0·086
			14	9·0	287	644	2·38	18·2	211	249	404	475	0·85	92	31·5	—	2·92	93	12	0·085
5122	28·6	12.11.18 11.30 a.m.	19·3	3·87	135	200	3·14	18·66	121	78	254	163	1·54	94	44	60	1·37	46	17	0·057
		3.45 p.m.	23·5	3·88	136	165	2·64	18·42	101	98	212	205	1·03	94	36	60	1·51	53	15	0·065
		14.11.18	22	5·34	187	243	2·49	18·85	132	95	276	199	1·38	92	40	52	1·90	66	20	0·050
		11.30 a.m.																		
3669	27·7	12.6.18 10.40 a.m.	13	4·03	146	310	3·06	16·8	122	177	264	385	0·69	88·5	35·5	56	2·88	104	16	0·0615
4444	27·2	26.8.18 6.45 p.m.	16·3	5·15	189	316	2·6	18·5	132	118	291	260	1·12	89	43	46	2·95	108	25	0·0400
		27.8.18 12 noon	17·5	7·93	292	453	2·92	18·9	232	137	512	302	1·70	100	49·5	52	2·56	94	19	0·0535
		7 p.m.	16	5·42	200	338	2·8	18·5	152	120	335	265	1·26	91	42	50	2·79	102	23	0·0430
		28.8.18 11.40 a.m.	15·6	5·05	186	324	2·66	18·7	134	102	295	225	1·31	98	51	54	2·08	77	20	0·0490
		5.35 p.m.	16	5·80	213	362	2·6	18·7	151	119	334	263	1·27	99	43	54	2·16	80	18	0·0550
3383	27·2	14.5.18 5 p.m.	21	7·54	278	360	2·70	18·0	201	224	445	482	0·90	94	48	77	3·38	124	15	0·066
3275	25·4	18.5.18 11 a.m.	19	6·57	259	346	2·84	17·8	184	205	436	486	0·90	87	48	60	4·77	188	23	0·043
		20.5.18 12 noon	24	7·51	297	313	2·87	18·1	214	211	567	500	1·01	97	39	60	3·34	132	16	0·063

TABLE I (*continued*).

Goat No.	Body Weight.	Date.	Respirations per min.	Expired Air, litres per min.	Expired Air, c.c. per kg. per min.	C.c. per Breath.	% CO_2 in Expired Air.	% O_2 in Expired Air.	Total CO_2 per min., c.c.	Total O_2 per min., c.c.	CO_2 per kg. per hour.	O_2 per kg. per hour.	R. Q. (corrected).	% Saturation, Arterial Blood.	% Saturation, Venous Blood.	Hb % on Human Scale.	Minute Volume, litres.	Min. Vol., c.c. per kg.	Min. Vol., c.c. per c.c. O_2 used.	O_2 difference, c.c. O_2 per c.c. blood.
5133	24·5 kg.	18.11.18 2.50 p.m.	18·7	6·80	277	364	3·50	17·40	238	240	586	588	0·99	97	43	61	3·90	159	16	0·0625
5086	23·6	19.11.18 10.50 a.m.	25	5·87	248	234	2·54	18·1	149	169	410	465	0·88	95	42	67	2·35	99	14	0·072
2952	23·6	2.5.18 10.15 a.m.	21	4·63	196	220	2·60	17·65	119	161	302	408	0·74	95	41	58	2·80	118	17	0·0575
2593	23·6	6.4.18	18	5·80	245	322	3·57	17·85	205	167	520	424	1·23	91	50	76	2·85	120	17	0·0583
		12.4.18 10.30 a.m.	17	4·85	205	285	2·92	18·3	140	121	355	307	1·16	92	51	68	2·35	100	19	0·0515
		13.4.18 3 p.m.	16	5·89	248	368	2·69	18·7	158	120	400	305	1·32	92	57	72	2·50	106	21	0·0477
2380	22·5	21.3.18 3 p.m.	19	6·30	280	332	2·74	18·4	171	151	456	403	1·13	101	59	62	3·00	134	20	0·0505
		28.3.18 3.30 p.m.	27	6·48	288	243	2·88	18·1	184	181	492	483	1·02	101	65·5	66	4·18	186	23	0·0434
		29.3.18 10.50 a.m.	27	7·51	334	278	2·70	18·4	200	182	533	485	1·10	96	43	66	2·78	124	15	0·0655
3326	22·4	25.5.18 11.15 a.m.	19	4·96	222	261	2·60	17·25	127	202	341	542	0·63	77	28	60	3·74	167	18	0·054
		27.5.18 10.45 a.m.	18	4·69	210	260	2·91	17·7	135	153	362	411	0·88	91	38	—	2·50	112	16	0·061
2181	22·3	21.2.18 2.50 p.m.	26	8·12	365	312	2·56	18·4	206	204	552	547	1·01	103	67	68	4·50	202	22	0·0452

TABLE I (*continued*).

Goat No.	Body Weight.	Date.	Respirations per min.	Expired Air, litres per min.	Expired Air, c.c. per kg. per min.	C.c. per Breath.	% CO_2 in Expired Air.	% O_2 in Expired Air.	Total CO_2 per min., c.c.	Total O_2 per min., c.c.	CO_2 per kg. per hour.	O_2 per kg. per hour.	R. Q. (corrected).	% Saturation, Arterial Blood.	% Saturation, Venous Blood.	Hb % on Human Scale.	Minute Volume, litres.	Min. Vol., c.c. per kg.	Min. Vol., c.c. per c.c. O_2 used.	O_2 difference, c.c. O_2 per c.c. blood.
4648	21·8 kg.	27.8.18 11 a.m.	14	5·06	232	361	2·9	17·8	147	160	404	440	0·92	98	50	65	2·66	122	17	0·060
		5.45 p.m.	14·2	4·65	213	257	4·07	17·6	189	142	519	390	1·33	90	41	67	2·25	103	16	0·063
		28.8.18 1.15 p.m.	11·6	5·95	272	512	4·1	17·8	244	166	670	456	1·47	93·5	30	64	2·39	105	14	0·072
		6.45 p.m.	14·8	3·36	154	227	3·92	16·8	132	139	362	382	0·95	93·5	38	62	2·10	96	15	0·066
		29.8.18 10.50 a.m.	13·6	3·20	147	235	3·72	17·0	119	127	327	349	0·94	97	41	61	2·05	94	16	0·062
2301	20·2	4.3.18 2.40 p.m.	19·3	3·03	151	157	3·52	17·0	106	121	314	360	0·88	97	51	68	2·11	105	18	0·0572
		5.3.18 11.50 a.m.	19·5	2·99	148	153	3·89	17·1	116	114	343	338	1·01	83	46	70	2·38	118	21	0·0478
		6.3.18 10 a.m.	19·3	3·16	157	164	3·36	17·1	105	122	314	363	0·86	94	52	68	2·30	114	19	0·0529
2288	19·5	13.3.18 10.5 a.m.	18	5·13	263	285	3·08	17·9	157	154	483	473	1·02	91	61	78	3·46	178	22	0·0445
		5 p.m.	18·5	5·26	269	285	3·23	18·0	168	147	519	469	1·14	97	62	75	2·96	152	20	0·0498
2720	18·4	12.4.18 3 p.m.	16	4·93	268	307	2·89	18·0	141	143	460	465	0·99	93	35	57	2·35	128	16	0·061
		13.4.18 10.30 a.m.	16	5·56	302	347	2·94	18·2	161	144	525	470	1·12	99	37	59	2·13	116	15	0·0677
2403	17·3	20.3.18 11 a.m.	20	4·07	235	204	3·77	16·75	152	175	521	608	0·87	89·5	44·5	75	2·64	153	15	0·066
		23.3.18 4.45 p.m.	23	3·50	202	153	3·43	17·1	119	137	412	476	0·87	106	51	69	2·19	126	16	0·0625
3171	17·3	15.5.18 11.50 a.m.	16	4·98	288	312	2·74	17·4	135	182	468	633	0·74	88	55	76	3·82	220	21	0·0478
2196	14·1	21.2.18 3.25 p.m.	19	4·76	338	244	2·84	17·9	134	144	570	613	0·93	96	42	60	2·40	170	17	0·0600

TABLE II.

Goat No.	No. of Experiments.	Sex.	Weight in kg.	Respirations per min.	Litres expired per min.	C.c. expired per kg. per min.	C.c. per Breath.	% CO_2 in Expired Air.	% O_2 in Expired Air.	Total CO_2 per min., c.c.	Total O_2 per min., c.c.	CO_2 per kg. per hour, c.c.	R. Q. (corrected).	% Saturation of Arterial Blood.	% Saturation of Venous Blood.	O_2 Difference, c.c. O_2 per c.c. Blood.	Hb % on Human Scale.	Min. Vol., litres.	Min. Vol. per kg., c.c.	Min. Vol. per c.c. O_2 used, c.c.
3632	(1)	F.	38·6	17	8·42	218	496	2·86	17·57	238	295	370	0·81	95·5	58	0·0525	78	5·60	145	19·0
3456	(2)	F.	31·4	14·5	9·25	295	638	2·65	17·86	243	289	466	0·84	94·5	30·75	0·0855	86	3·37	107	11·7
5122	(3)	F.	28·6	21·6	4·36	153	203	2·76	18·64	118	90	287	1·32	93·1	40	0·0573	57	1·59	55	17·7
3669	(1)	F.	27·7	13	4·03	146	310	3·06	16·8	122	177	264	0·69	88·5	35·5	0·0615	56	2·88	104	16·3
4444	(5)	F.	27·2	16·3	5·87	216	359	2·72	18·66	160	119	353	1·33	95·4	45·7	0·0481	51	2·51	92	21·2
3383	(1)	F.	27·2	21	7·54	278	360	2·70	18·0	201	224	445	0·90	94	48	0·066	77	3·38	124	15·1
3275	(2)	F.	25·4	21·5	7·04	278	329	2·85	17·95	199	208	471	0·95	92	43·5	0·0530	60	4·05	160	19·4
5133	(1)	F.	24·5	18·7	6·80	277	364	3·50	17·40	238	240	586	0·99	97	43	0·0625	61	3·90	159	16·3
5086	(1)	F.	23·6	25	5·87	248	234	2·54	18·1	149	169	410	0·88	95	42	0·072	67	2·35	99	13·9
2952	(1)	F.	23·6	21	4·63	196	220	2·60	17·65	119	161	302	0·74	95	41	0·0575	58	2·80	118	17·4
2593	(3)	M.	23·6	17	5·51	233	325	3·06	18·28	168	136	425	1·24	91·7	52·7	0·0525	72	2·57	109	18·9
2380	(3)	F.	22·5	24·3	6·76	301	284	2·77	18·30	185	171	494	1·08	99·1	55·8	0·0531	65	3·32	148	19·4
3326	(2)	F.	22·4	18·5	4·82	216	260	2·75	17·47	131	177	351	0·75	84	33	0·0575	60	3·12	139	17·6
2181	(1)	F.	22·3	26	8·12	365	312	2·56	18·4	206	204	552	1·01	103	67	0·0452	68	4·50	202	22·1
4648	(5)	F.	21·8	13·6	4·44	304	318	3·74	17·4	166	147	456	1·12	94·4	40	0·0646	64	2·27	104	15·5
2301	(3)	M.	20·2	19·4	3·06	152	158	3·59	17·07	109	119	324	0·92	91·3	49·7	0·0526	69	2·26	112	19·0
2288	(2)	F.	19·5	18·2	5·19	266	285	3·15	17·95	162	150	501	1·08	94	61·5	0·0471	76	3·21	165	21·4
2720	(2)	F.	18·4	16	5·24	335	327	2·91	18·10	151	143	492	1·05	96	36	0·0643	58	2·24	122	15·6
2403	(2)	F.	17·3	21·5	3·78	218	178	3·60	16·92	135	156	466	0·87	97·7	47·7	0·0642	72	2·41	139	15·5
3171	(1)	F.	17·3	16	4·98	288	312	2·74	17·4	135	182	468	0·74	88	55	0·0478	76	3·82	220	21·0
2196	(1)	F.	14·1	19	4·76	338	244	2·84	17·9	134	144	570	0·93	96	42	0·0600	60	2·40	170	16·7
	Mean		23·67	19·0	5·737	253	310	2·95	17·80	165	176	424	0·96	94·0	46·1	0·0583	66·2	3·07	133·0	17·65
	σ		5·31	3·52	1·60	60·5	103·4	0·38	0·51	40·8	40·8	94·4	107	0·18	3·952	9·75	0·0062	9·09	0·904	37·3	2·61
	v		22·4 %	18·6 %	28·0 %	23·9	33·3	13·0 %	2·89	29·2	23·2	22·3 %	23·5	18·8 %	4·2	21·1	16·9 %	13·7	29·5	28·0	14·8 %

Defect of O_2: 3·14, 0·51, 16·4 %.

MEASUREMENT OF PRESSURE CHANGES IN THE RIGHT VENTRICLE BY CARDIAC PUNCTURE

By JOHN SHAW DUNN

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THE methods which are usually employed for registering fluctuations in the endocardial pressure entail serious operative measures of a nature which renders successive examinations in the same animal difficult or impossible. In the present communication it is proposed to describe a simple procedure whereby a series of records of endocardial pressure may be obtained at intervals extending over several days without endangering the life of the animal. The method has the special advantages that no anaesthetic is required, operative measures are reduced to a minimum, and artificial respiration is dispensed with. Between the examinations the animal leads a practically normal existence. The method as it has been employed comprises the use of a tambour and lever for recording, so that it is applicable to the study of gross alterations in the general pressure rather than to accurate registration of the rapid changes which occur during each cardiac cycle.

Goats have been used exclusively in the experiments, and have been found very suitable for various reasons. They are of comparatively large size (20–30 kilos), and the position of the heart is easy to define accurately: they are also easy to handle and exhibit great indifference to minor operative measures. An experiment is carried out in the following way: The goat is laid on its right side on the operating table. A 5 c.c. Record syringe is fitted with a needle of about 0·75 mm. bore and $1\frac{3}{4}$ to 2 inches long: the syringe and needle are washed out with a 10 per cent. solution of sodium citrate, and the bore of the needle remains filled with this fluid. The needle is thrust through the skin and thoracic wall until it touches the heart, and is then pushed through the cardiac muscle into the cavity. In a normal goat of average size the point selected for puncture is in the third left interspace, about three finger-breadths or a little less from the anterior aspect of the sternum, and the needle is directed vertically. In the great majority of instances the right ventricle is thus easily reached at a depth of $1\frac{1}{4}$ to $1\frac{1}{2}$ inches. The success of the puncture is ascertained by gently withdrawing the piston of the syringe, when venous blood ascends into the barrel. The syringe is then detached from the needle and the free end of a piece of

[Q. J. M., Oct., 1919.]

pressure tubing, filled with 10 per cent. citrate, is slipped over the needle boss. The other end of the rubber tube, which is 40 cm. in length, is attached to the tambour chamber of a Hürthle manometer, also filled with the citrate. When the tap of the tambour is opened the lever oscillates in response to the cardiac pulsations and the oscillations are recorded on smoked paper on a revolving drum. After a tracing has been taken it is necessary to draw a zero line: this is obtained by detaching the rubber tube from the needle, the latter having been withdrawn from the heart, and holding the free end of the tube at the level of the needle-point when the latter was in the ventricle. From the zero line a scale can then be built up by raising the free end of the rubber tube to successive distances of 5, 10, 15, &c., cm. above the zero. As the tube is raised the tambour lever rises in response to the rise of pressure and the various pressures in c.c. of citrate are marked on the tracing. From this scale it is possible later to estimate the pressure in mm. of mercury corresponding to any point on the tracing or to calculate mean systolic or diastolic pressures. It has been customary to make a scale for each separate tracing in order to eliminate fallacies which might arise from changes in the tambour membrane.

A tracing of the respiration is taken simultaneously with the blood-pressure record. The apparatus used for this is a rubber football bladder bandaged on to the thorax of the goat and connected to a recording tambour. This shows the rate and time incidence of the respirations, but gives no information as to depth. The beats of the time-marker on each record indicate seconds.

The procedure of puncturing the heart as outlined above can be carried out very readily and successfully in the great majority of normal goats. Difficulty arises in animals which struggle, as some do even when placed on the operating table. It is best to avoid the use of such. Struggling, however, is most likely to occur just when the skin and the parietal pleura are punctured, and it is then advantageous to wait a few seconds before pushing the needle farther. The heart itself appears to be insensitive to the needle.

There are two important accidental lesions which may be produced in attempting to reach the ventricle, and one or other is certain to occur from time to time, even with the best technique. One is pneumothorax, caused by tearing the edge of the lung: this is never fatal to the life of the animal, but it may interfere with the object of the experiment for other reasons. The other is haemopericardium, due to injury of a branch of a coronary vessel: bleeding apparently never comes through the puncture from the ventricle itself. The risk of haemopericardium is minimized by pushing the needle-point sharply through the muscular wall as soon as the cardiac surface is reached: damage is done if the point scrapes the visceral pericardium. Both accidents are most liable to occur if there is struggling, but neither has proved a frequent or serious complication in the normal goat.

A typical normal tracing is shown in Fig. 1. The waves corresponding to each systole occur at regular intervals and are of approximately equal height. In each the rise is steep and the summit is sustained in the form of a plateau.

It is evident that the pulse and respiration are very little disturbed by the operation of passing the needle into the heart. The respiratory undulations are visible on the blood-pressure tracing, each inspiration being accompanied by a slight fall of systolic and diastolic pressure. The mean systolic pressure here corresponds to 22·0 mm. of mercury, the maximun being 23·0 and the minimum 21·0 mm.

A record taken with the drum moving at a rapid rate gives systolic waves of the same height. This tracing brings out the fact that during almost the whole of diastole the line is truly horizontal. If the curve were damped by friction in the needle or inertia in the system one would not obtain a tracing of this type. We conclude, therefore, that the lowest point of the tracing represents the lowest pressure which exists in the right ventricle and that the summit of the tracing gives an accurate reading of the systolic pressure.

Tracings taken from fifteen normal goats have given blood-pressure curves very similar in general outline to that depicted in Fig. 1, but there are individual variations in the average pressures, and in the extent to which the pressures are influenced by respiration. The mean pressures and the maxima and minima are given in the following table:

Goat No.	Resp. Rate.	Systolic Pressure.			Diastolic Pressure.		
		Mean.	Maximum.	Minimum.	Mean.	Maximum.	Minimum.
D 28	24	14·0	22·0	10·0	1·0	5·0	−4·0
D 25	16	15·5	16·5	12·5	1·0	4·5	−4·0
D 37	24	15·5	17·0	14·0	1·5	4·5	−2·0
D 39	18	17·5	19·0	15·0	2·0	4·5	−1·0
D 22 b	22	9·5	13·0	7·0	2·5	6·0	0·0
D 42	22	15·5	17·0	13·0	2·5	5·5	0·0
D 35	22	19·0	23·5	15·0	3·0	8·0	−1·5
D 39 a	16	22·0	23·0	21·0	5·0	6·0	4·0
D 30	22	23·5	26·0	16·0	5·0	9·5	1·0
D 27	14	21·5	22·0	19·5	5·5	6·0	4·5
D 31	26	15·0	17·0	13·0	5·5	6·0	1·0
D 40	34	18·0	19·5	17·0	5·5	6·0	4·0
D 26	13	21·5	26·0	20·0	6·0	8·5	4·0
D 36	16	22·0	26·5	16·5	6·0	12·5	4·0
D 23	18	27·5	29·0	26·0	11·5	15·0	8·5

The mean systolic pressure, which is taken to represent the mean pressure in the pulmonary artery, varies in different animals between the extremes of 9·5 and 27·5 mm. of mercury, and the average for the fifteen is 18·5 mm. Thirteen out of the fifteen lie between 14·0 and 23·5 mm. The goat with the low figure of 9·5 mm. gave 11·0 mm. on another examination, indicating an habitually low pressure. The highest pressure observed, 27·5 mm., appears to have been exceptional even in the animal which showed it, for on other occasions it had a pressure of 16·5 and 20 mm. The curves from which these pressures have been calculated generally show flat-topped waves with a well-defined limit to each plateau, as in Fig. 1, so it may be safely assumed that there is no overthrowing of the tambour lever and that the pressures given do not err by being too high.

'The mean pressure in the pulmonary artery collected by Tiegerstedt amounts

in the rabbit to 12 mm., in the cat to 18 mm., and in the dog to 20 mm.' (Fuhner and Starling, *Journ. Phys.*, xlvii, p. 288).

The results obtained from the unanaesthetized goat correspond, therefore, to those given above for the dog and cat, and are slightly higher than the average (14 mm. mercury) obtained by Fuhner and Starling in the heart-lung preparation. Their statement, however, that the pressure in the pulmonary artery is one-sixth of the systemic arterial pressure is substantially confirmed.

The mean diastolic, like the mean systolic pressures, exhibit a considerable range of variation, from 1·0 to 11·5 mm., but are always above zero level. The average for the fifteen animals is 4·2 mm. of mercury. In five out of fifteen the minimum diastolic pressure falls below zero, and in two of these the negative pressure amounts to 4·0 mm., which is probably well outside the range of experimental error. The negative pressures occur in diastolic periods which coincide with the rise of inspiration, when the intrathoracic pressure is lowest and the ventricular well relaxed.

No reason has been found to account for the variations in the mean pressures in different animals. From the table it appears that the lower diastolic pressures do not run parallel with the higher rates of respiration, though this appeared a probable relationship. Negative diastolic pressures have been much more frequently observed in animals which were breathing rapidly and forcibly as a result of experimental lesions.

The mean diastolic pressure in the right ventricle may be assumed to differ but little from the pressure in the large veins, as there is no intervening valve. The blood-pressure in the external jugular vein has been actually measured in sixteen normal goats and the results are set out below for comparison. The measurements were made by a U-manometer filled with 10 per cent. citrate solution, and the vein was reached by puncturing through the skin with a wide-bore needle. The pressures observed in these animals were as follows:

Number of Goats.	Venous Pressure in mm. Hg.
1	2·0
5	3·0
3	3·5
4	4·5
1	5·0
2	6·0
Total 16	Mean 3·9 mm.

The mean pressure, 3·9 mm., obtained by this method compares with 4·2 mm. observed in the ventricle in the fifteen other animals, and the range of variation is fairly similar. The citrate manometer allows of prolonged observation and of very accurate measurements, so that these figures help to confirm the approximate correctness of the pressures observed in the ventricle by cardiac puncture.

Normal tracing. In the normal tracing shown in Fig. 1 the respiratory curve is not precisely above the cardiac curve. The arcs at the commencement of the tracings show the relative positions of the writing-points when the drum is at rest. Taking this fact into consideration it appears that the lowest point on the

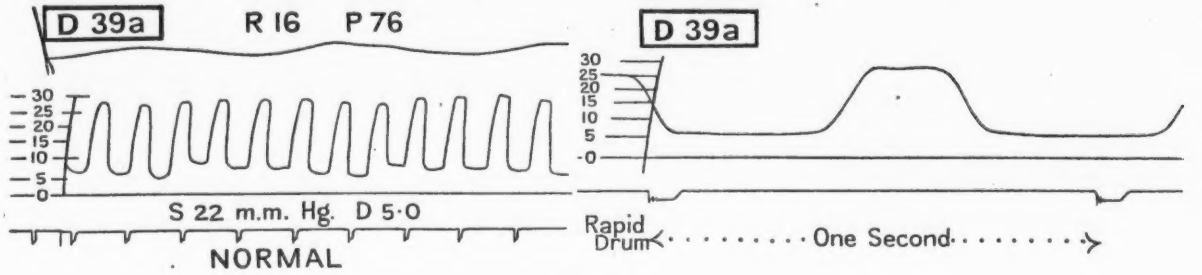


FIG. 1.

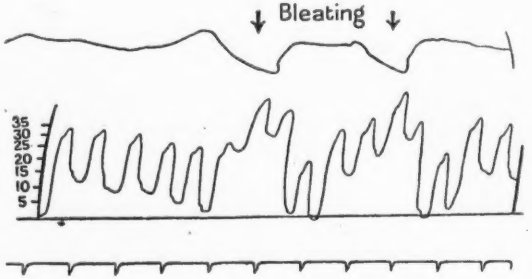


FIG. 2.

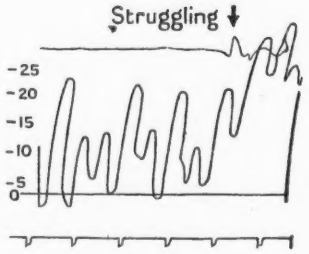
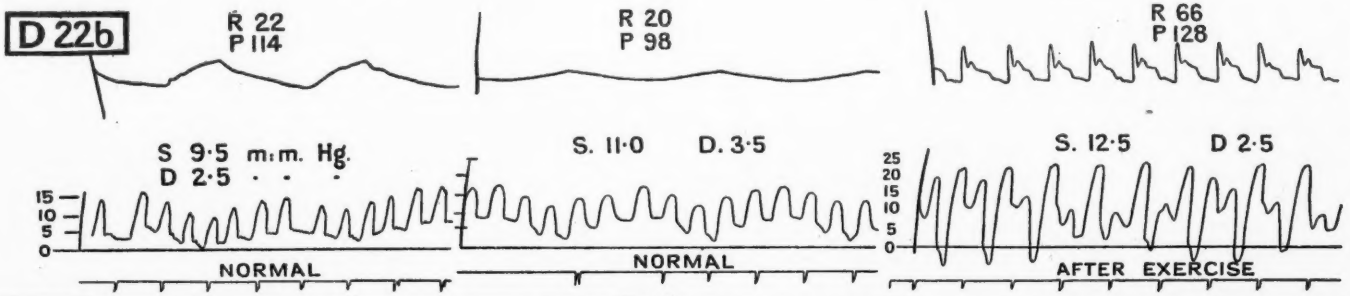


FIG. 3



curve of both the systolic and diastolic pressures is synchronous with the height of inspiration. This fact is in contrast with the conditions on an arterial blood-pressure curve, where the height of inspiration takes place appreciably before the lowest point is reached on the respiratory undulation of the blood-pressure. It would appear, therefore, that the lag shown on the systemic blood-pressure curve is not due to any event communicated through the heart, such as, for instance, the forcing of blood into the great veins by increased pressure in the abdomen, but is due to events taking place in the thorax itself.

Effect of exercise. Measurements of the ventricular pressure were made in two goats before and immediately after exercise. The animals were induced to run twice up and down a steep gradient about seventy yards long: this was only accomplished after considerable difficulty, the result being that the goats were much less exercised than the experimenters. One of the tracings, however, shows a considerable acceleration of the respiration (Fig. 4). The first two sections are from the normal resting animal, and show the usual characters, although the mean systolic pressures are unusually low. The minimum diastolic pressure in one reaches the zero line, but does not fall below it. After exercise the respiration has risen to 66 per min. from 22/20, and the pulse to 128 from 114/98.

There is a remarkable change in the form of the blood-pressure curve, due to the alteration in cardio-respiratory ratio. The inspirations occur a little more than half as rapidly as the systoles, so that the influence of each inspiration falls successively a little earlier on every second cardiac cycle. The effect of this is best observed by drawing a line through the apex of every second systole: this line exhibits a slow regular undulation or 'beat' such as results from interference between any two series of vibrations which have nearly but not quite the same amplitude.

The mean, maximal, and minimal pressures in the three sections of the tracing are as follows:

		Systole.			Diastole.		
		Mean.	Maximum.	Minimum.	Mean.	Maximum.	Minimum.
Normal	(1)	9·5	13·0	7·0	2·5	6·0	0·0
	(2)	11·0	12·5	8·5	3·5	6·0	1·5
Exercise		12·5	18·0	8·0	2·5	8·0	−4·0

After exercise the range between maximal and minimal pressures is considerably extended, and the minimum diastolic pressure is below zero. This negative pressure is produced at points where diastole coincides with inspiration, so that the strongest negative intrathoracic pressure is acting on a relaxed ventricular wall. In spite of these greater fluctuations of pressure it will be observed that the mean systolic and diastolic pressures are hardly altered from the normal.

In the other exercise experiment (Fig. 5) the acceleration of respiration is much less, and the only change in the tracing is a slight accentuation of the respiration wave on the blood-pressure curve; the mean pressures are hardly affected.

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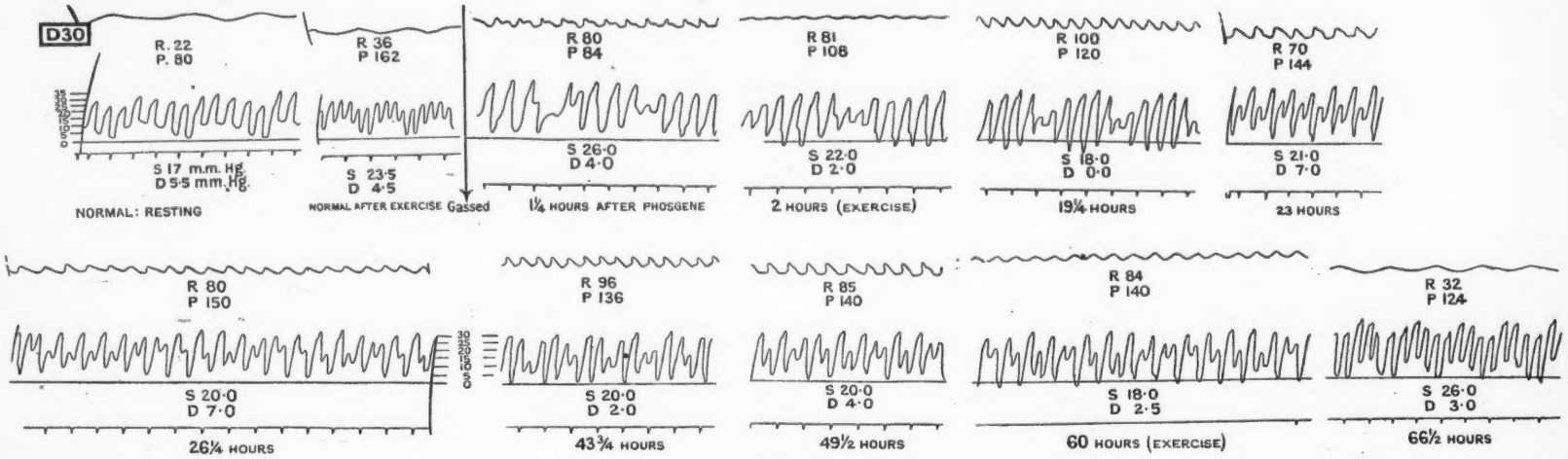
D30
R. 22
P. 80
S 17 m.m. Hg.
D 5·5 mm. Hg.
NORMAL: RESTING
R 36
P 162
S 23·5
D 4·5
NORMAL AFTER EXERCISE
Gassed
R 80
P 84
S 26·0
D 4·0
1¼ HOURS AFTER PHOSGENE
R 81
P 108
S 22·0
D 2·0
2 HOURS (EXERCISE)
R 100
P 120
S 18·0
D 0·0
19¼ HOURS
R 70
P 144
S 21·0
D 7·0
23 HOURS
R 80
P 150
S 20·0
D 7·0
26¼ HOURS
R 96
P 136
S 20·0
D 2·0
43¾ HOURS
R 85
P 140
S 20·0
D 4·0
49½ HOURS
R 84
P 140
S 18·0
D 2·5
60 HOURS (EXERCISE)
R 32
P 124
S 26·0
D 3·0
66½ HOURS

FIG. 5.

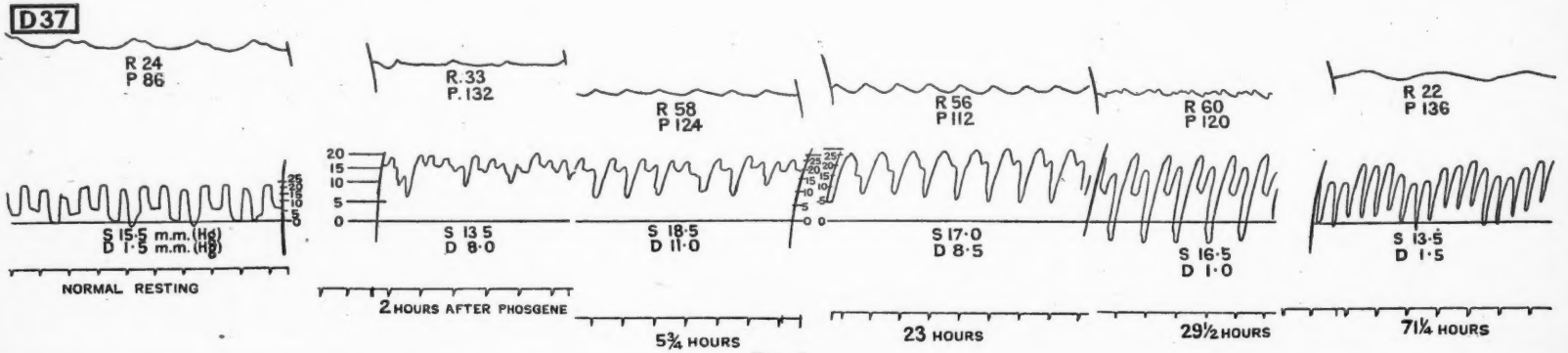
D37
R 24
P 86
S 15·5 m.m. (Hg)
D 1·5 m.m. (Hg)
NORMAL RESTING
R. 33
P. 132
S 13·5
D 8·0
2 HOURS AFTER PHOSGENE
R 58
P 124
S 18·5
D 11·0
5¾ HOURS
R 56
P 112
S 17·0
D 8·5
23 HOURS
R 60
P 120
S 16·5
D 1·0
29½ HOURS
R 22
P 136
S 13·5
D 1·5
71¼ HOURS

FIG. 6.

Effects of bleating and struggling. When struggling occurs while a tracing is being taken there is an immediate and very marked alteration in the blood-pressure curve. Examples of this are given in Figs. 2 and 3. Fig. 2 shows the effect of bleating: the animal was normal when it was under examination, and gave mean pressures of 17·0 mm. systolic, and 5·5 mm. Hg diastolic. During the periods when the animal made the violent expiratory efforts of bleating the diastolic pressure was raised to 22 mm. Hg. Fig. 3: this animal was under examination at a period two hours after exposure to phosgene. The mean pressures were almost the same as had been obtained from the normal animal, viz. systolic 11·5 mm. and diastolic 1·0 mm. When struggling occurred the diastolic pressure rose at once to 18·0 mm. Hg. In both these cases the same factor is no doubt responsible for the change: the diaphragm was fixed during the muscular effort and the intrathoracic pressure was raised by forcible expiration, so that the pulmonary circulation was partially obstructed, and a rise of pressure ensued.

Effects of phosgene poisoning. Tracings of the blood-pressure in the right ventricle were taken from a number of goats before and after exposure to phosgene gas. In these gassed animals the rapid and forcible respiratory movements rendered it difficult to perform the cardiac punctures successfully, and when, as occasionally happened, there was much struggling the attempt had to be abandoned. The experiments were especially apt to fail when high doses of gas had been administered. In the following cases it was possible to carry out several successful examinations, and post mortem there was found no serious pericardial bleeding or pneumothorax, such as might have aggravated or modified the phenomena due to gas poisoning.

Experiment D 30. Phosgene poisoning, with recovery. The goat was exposed to phosgene, 1 part in 5,000 by volume, for ten minutes, and soon after removal from the gas chamber it had developed severe dyspnoea, with a respiration-rate of 80 per minute. The dyspnoea continued, and between twenty and thirty hours after gassing the animal passed through its most critical period, the pulse-rate rising to 150 per minute. Afterwards the symptoms lessened, and on the third day the respiratory rate fell to 32 per minute. Recovery had obviously set in and the animal was killed, so that the extent of the pulmonary lesion might be observed. On post-mortem examination there was found extensive oedema in the ventral half of each lung, and it was evident that oedema had been more abundant at an earlier period. The appearances were those of a gas casualty of moderate severity in process of resolution.

The tracing (Fig. 5) shows first a section taken from the normal animal at rest, and next one after exercise. Then follow nine separate sections at intervals after exposure to gas. At 1¼, 2, and at 19¼ hours after gassing the tracing shows rhythmical fluctuation in the blood-pressure curve, due to alterations in the cardio-respiratory ratio, the effects being similar to those of heavy exercise. The maximum systolic pressures are raised and the minimum diastolic pressures are lowered even to negative values, but the mean pressures are not very conspicuously altered: there is actually a slight diminution in the mean diastolic pressure. At 23 and at 26¾ hours the fluctuations due to respiration are still well marked, but now there is a slight rise in the mean diastolic pressure above the normal: this coincides with the period of most critical illness. In the

FIG. 6.
5¾ HOURS

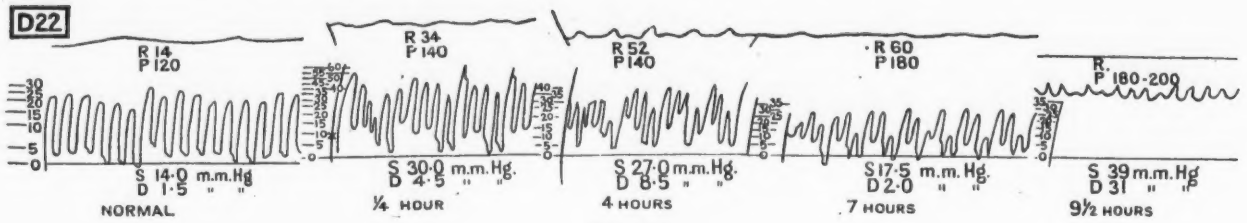

FIG. 7.

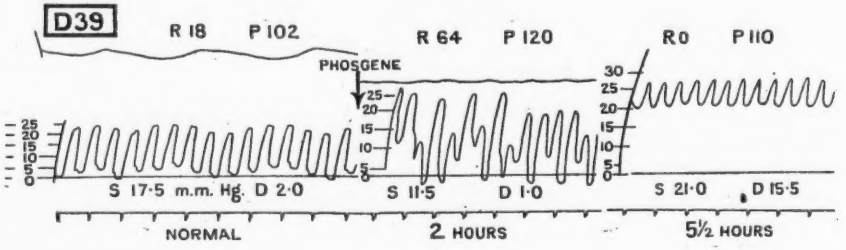

FIG. 8.

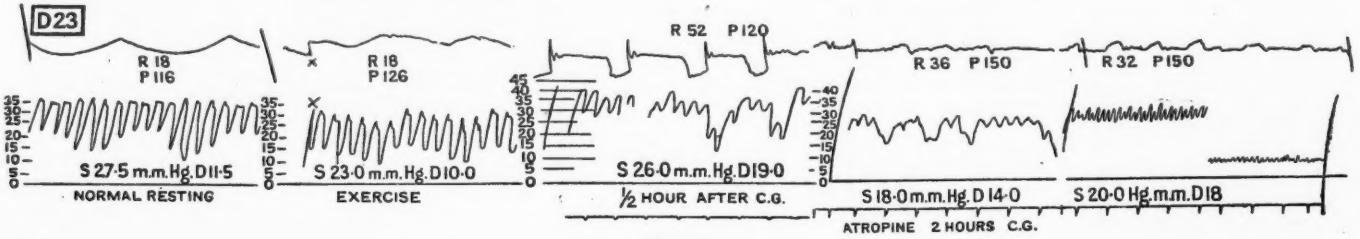

FIG. 9.

later sections of the tracings the mean diastolic pressure has fallen again, and at 66½ hours the blood-pressure curve is reassuming normal characters.

A series of measurements of the volume of blood circulating per minute[1] was made in this experiment, with the following results:

Normal resting	2660 c.c. per min.	26½ hours after gassing	2820 c.c. per min.
Normal after exercise	5260 „	43¾ hours after gassing	5410 „
1¼ hours after gassing	2940 „	49½ hours after gassing	3780 „
2 hours after gassing (exercise)	3870 „	51 hours after gassing (exercise)	3780 „
19¼ hours after gassing	4600 „	66½ hours	3950 „
23 hours after gassing	2160 „		

Experiment D 37. Phosgene poisoning with recovery. After having been examined in the normal condition at rest, this goat was exposed to 1/4,000 phosgene for ten minutes. Two hours after gassing the respiratory rate had risen to only 33 per minute from 24. The breathing was very shallow, each respiration amounting to 120 c.c. instead of the normal of about 300 c.c. A sample of the arterial blood taken at two hours showed a severe anoxaemia, the oxygen saturation being only 57 per cent. In other goats examined two hours after the same dose of gas the arterial blood has been saturated to about 90 per cent. like the normal.

Five hours after gassing the respiratory rate had risen to 56 per minute, and the oxygen saturation of the arterial blood was 94 per cent., showing that the cause of the anoxaemia was something of a transient nature. The dyspnoea with rapid respiratory rate continued for forty-eight hours, but during this period there was no recurrence of the severe anoxaemia. On the third day the respiratory rate had fallen to 22 per minute. The animal was then killed. Post mortem the lungs were almost free from oedema and the appearances were such as to indicate that oedema had never been severe. It was considered most probable that this animal suffered from bronchiolar spasm in the early hours after gassing, with temporary severe anoxaemia as a result.

The tracing (Fig. 6) shows a very definite rise in the mean diastolic pressure during the first twenty-four hours after gassing, but very little change in the mean systolic pressure. The influence of the increased respiratory rate on the blood-pressure curve is well marked. The section of tracing taken on the third day is approaching the normal condition.

Experiment D 22. Fatal phosgene poisoning. The goat was exposed to 1/5,000 phosgene for ten minutes. The usual symptoms of dyspnoea and cardiac distress developed rapidly, and in nine hours the animal was in a critical condition and unlikely to live for more than two or three hours longer. When it was placed on its side for examination at 9½ hours the breathing rapidly weakened and became gasping in character, and death occurred in a few minutes. On post-mortem examination the lungs exhibited severe oedema of almost universal distribution, the appearances being typical of fatal phosgene poisoning.

The tracing (Fig. 7) shows one section taken from the normal resting animal and four others at intervals after exposure to gas. A quarter of an hour after gassing there is a considerable rise in the systolic pressure, to 30 mm. of mercury, and a slight rise in diastolic pressure. At four hours the rise of systolic pressure is maintained and the diastolic pressure is definitely raised above the normal to 8·5 mm. Hg. Seven hours after gassing the mean pressures have fallen again almost to normal, although the condition of the animal is much worse, the pulse-rate being 180 per minute. At nine and a half hours the respiration has almost ceased, and there is only an occasional gasping inspiration. At this time the blood-pressure in the ventricle remains continuously at a great height, more than

[1] The rate of blood flow in gas poisoning will form the subject of a subsequent communication.

30 mm. Hg, and there is relatively little difference between systolic and diastolic pressures.

In this instance, coincident with a more rapid and severe clinical course, there is a definite rise in both systolic and diastolic pressures up to four hours after gassing. This probably arises from the adverse effect of the gas lesion on the pulmonary blood-vessels. The meaning of the fall in pressure at seven hours is not understood. The last section of the tracing represents a terminal phase in a moribund animal, and it is not certain that this condition of permanently raised pressure is peculiar to death from gas poisoning. The high pressure may be in part determined by diminished permeability of the pulmonary vessels, but an important factor must also be the absence of the support which is normally afforded to the pulmonary circulation by respiratory movements. An exactly parallel result has been obtained in another gassed animal in the act of death.

Experiment D 39. Fatal phosgene poisoning. The goat received a dose of 1/4,000 phosgene for ten minutes. Dyspnoea developed at once and in two hours was very severe, the respirations numbering 64 per minute. At 5½ hours the animal was very ill and death was precipitated by turning it on its side for examination. At post-mortem examination the lungs were extremely oedematous, the condition being such as might occur in an animal dying after phosgene poisoning without being subjected to further handling.

The tracing (Fig. 8) shows a normal curve of the usual type. Two hours after gassing the curve is irregular on account of the rapid respiration, but there is no change in the mean diastolic pressure. At five and a half hours the respiration has stopped, but the heart continues to beat. As in the previous experiment the ventricular pressure is continuously very high at this examination.

These four experiments with gas poisoning show differences depending on the severity of illness in the different animals and on the times of examination. Nos. D 30 and 39 show that severe dyspnoea may be developed without the ventricular pressures being materially altered. Nos. 30, 37, and 22 show a definite rise in mean diastolic pressure at certain intervals after gassing, and in two of these the pressures subside to normal as recovery sets in. The very high ventricular pressures observed at the time of death in Nos. 22 and 39 are probably terminal only, and cannot certainly be taken to represent the conditions which existed shortly before, while the animals were still breathing. The most critical state of illness which it has been possible to examine by this method in an animal still breathing is represented in the fourth section of Fig. 9, and there the mean diastolic pressure 14 mm. is separated by only 4 mm. from the systolic pressure.

The work embodied in this communication was carried out at the suggestion of Mr. Joseph Barcroft, F.R.S., and under his direction. The writer has to express to him most cordial thanks for helpful advice and criticism.

THE EFFECT OF EXPERIMENTAL PLEURAL EFFUSION ON THE BLOOD-PRESSURE IN THE RIGHT VENTRICLE

By JOHN SHAW DUNN

(From the Physiological Department, R.E. Experimental Station, Porton)

With Plate 1

In these experiments the blood-pressure in the right ventricle was measured by passing a hollow needle through the skin and thoracic wall into the ventricular cavity, and connecting the needle to a Hürthle manometer by pressure-tubing. Continuity between the blood in the ventricle and the tambour membrane of the manometer was established by filling the rubber tube and tambour with a solution of 10 per cent. sodium citrate. The procedure has been fully described in another communication.

Pleural effusion was produced by infusing a quantity of defibrinated blood from another animal of the same species into one or other pleural cavity, usually the right. Such an infusion might be referred to as a haemothorax, but the latter term implies haemorrhage into the thoracic cavity from the animal's own vessels, usually from a wound in the lung, and this was not the condition reproduced here.

The animals employed were goats. Four experiments were performed, using different quantities of blood. In each case an examination was made on the normal animal, and one or more at intervals after infusion of blood into the pleura. The effects on the rate of pulse and respiration and on the mean systolic and diastolic pressures are stated below in tabular form. The ventricular pressures were measured originally in centimetres of 10 per cent. sodium citrate, but are stated here in millimetres of mercury.

	Pulse-rate.	Respiration-rate.	Mean Ventricular Pressures in mm. Hg.	
			Systolic.	Diastolic.
Goat D 26. Weight, 22·2 kilos. 800 c.c. blood into left pleura (Fig. 1).				
Normal	82	13	21·5	5·5
After infusion—				
1¼ hours	88	33	23·5	11·0
18 hours	96	22	22·5	9·5

	Pulse-rate.	Respiration-rate.	Mean Ventricular Pressures in mm. Hg.	
			Systolic.	Diastolic.
Goat D 27.				
Weight, 22·7 kilos.				
1,350 c.c. blood into right pleura (Fig. 2).				
Normal	68	14	21·5	5·5
After infusion—				
35 minutes	120	40	23·5	10·0
23 hours	120	40	25·5	6·0
41½ hours	124	28	22·0	6·0
65½ hours	100	46	20·5	7·0
6 days	100	32	16·5	3·0
Goat D 31.				
Weight, 21 kilos.				
1,350 c.c. blood into right pleura (Fig. 3).				
Normal	95	26	15·0	5·5
After infusion—				
50 minutes	200	40	40·0	25·0
20½ hours	140	60	15·5	6·0
Goat D 35.				
Weight, 26·4 kilos.				
1,000 c.c. blood into right pleura (Fig. 4).				
Normal	116	22	19·0	3·0
After infusion—				
10 minutes	140	40	19·5	11·5
16½ hours	124	56	24·0	10·0

The course of illness and the pathological changes in the four experiments were briefly as follows :

D 26. After introduction of blood into the pleura the animal developed a moderate degree of dyspnoea, but the pulse-rate was unaffected. After eighteen hours the dyspnoea had almost entirely subsided. The goat was not killed immediately, the experiment being continued by introducing air into the pleura.

D 27. A considerable degree of dyspnoea developed after infusion of blood into the thorax, and this continued severe for twenty-four hours. The pulse-rate rose to 120 per minute and continued high. The oxygen saturation of arterial and venous blood was measured each time the heart was punctured, the results being as follows :

After Infusion of Blood.	Arterial.	Venous.
	%	%
35 minutes	88	47
23 hours	84	52
41½ hours	74	31
65½ hours	79	59
6 days	98	61

The figures show some desaturation during the first three days, and the normal condition is restored by the sixth day. The animal was killed after the last examination. The right pleura contained 300 c.c. of blood. There were patches of airless collapse in the dependent parts of the right lung, but the organ

as a whole was well aerated; there had, no doubt, been more extensive collapse at an earlier period.

D 31. This animal had pronounced dyspnoea, the breathing being difficult rather than rapid. The pulse-rate rose to 200 per minute. When an attempt was made to puncture the heart at twenty hours the animal collapsed and almost died: it was resuscitated by withdrawing 400 c.c. of blood from the pleural cavity. The symptoms continued, however, and death occurred twenty-seven hours after the commencement of the experiment. Post mortem 1,000 c.c. of blood were found in the right pleura, and the right lung was completely collapsed and airless. There was also slight general collapse and much congestion of the left lung. There was much haemorrhage into the mucous membrane at the lower end of the trachea.

D 35. Dyspnoea and cardiac embarrassment were marked after blood was introduced into the thorax. The oxygen saturations of arterial and venous blood were as follows at the various examinations:

	Arterial.	Venous.
	%	%
Normal	94	47
After infusion, 10 minutes	76	35
„ „ 16½ hours	83	51

Death occurred between thirty and thirty-six hours after the commencement of the experiment. Post mortem 1,350 c.c. of blood were recovered from the right pleura. The right lung was completely collapsed and airless, and there was slight general collapse of the left lung.

The most important change observed in all the experiments was the rise in mean diastolic pressure in the right ventricle. This was found at the first examination after the pleural effusion had been produced, and in two instances it was maintained at eighteen and at sixteen and a half hours respectively. It had subsided at twenty-three hours in D 31, which was recovering, and also at twenty and a half hours in D 35, which was dying. The rise in mean diastolic pressure is believed to be due to diminution of the negative pressure in the thorax. The introduction of fluid into the pleura brings the thorax nearer to the condition of full expansion, and so diminishes the extent to which the inspiratory muscles may act, and lessens their power to produce negative intrathoracic pressure.

It was only in one goat, D 31, which received the largest volume of fluid, that there was any considerable rise in the mean systolic pressure, which must represent the pressure in the pulmonary artery. Here we have evidence that the bulk of fluid in the pleura was sufficient to cause actual obstruction to the pulmonary circulation.

The analyses of arterial blood in two experiments are important, as they indicate that some part of the pulmonary circulation was continued through collapsed lung, where no aeration could take place.

Description of Figures.

Figs. 1 to 4 are the tracings of ventricular pressure in these experiments. In each there is a section showing the normal state, and two or more sections taken at intervals after production of pleural effusion. On each section is noted the pulse- and respiration-rate and the mean systolic and diastolic pressures for that period. The scales at the ends of the tracings represent pressure measured in cubic centimetres of 10 per cent. sodium citrate.

Effect of Pneumothorax on the Blood-pressure in the Right Ventricle.

Experimental pneumothorax was produced in two goats, and the effects on the blood-pressure in the right ventricle were observed by puncturing the heart with a hollow needle and connecting the latter to a Hürthle manometer.

Experiment D 25. Goat, weighing 18 kilos (Fig. 5).

A tracing was taken from the normal resting animal, and later a hollow needle of wide calibre was passed into the left pleura, and air was allowed to enter the cavity at atmospheric pressure as the lung collapsed. At the end the air blew out and in through the needle with the respiratory movements. The animal suffered no obvious discomfort. The rate of respiration rose from 16 to 24 per minute, and the pulse-rate from 90 to 130. A second tracing was taken twenty minutes after pneumothorax had been produced.

The alterations in the mean systolic and diastolic pressures were as follows:

	Mean Pressures in Right Ventricle: mm. Hg.	
	Systolic.	Diastolic.
Normal	15·5	1·0
20 minutes after pneumothorax	20·0	12·0

The striking alteration was the considerable rise in the mean diastolic pressure from 1·0 to 12·0 mm. of mercury. The mean systolic pressure was also raised, but to a less extent.

Experiment D 26. Goat, weighing 22·2 kilos (Fig. 1).

This animal had already had 800 c.c. of blood infused into the left pleural cavity, with the result of causing a considerable rise in the mean diastolic pressure. Eighteen and a half hours afterwards a hollow needle was passed into the right pleura and 1,000 c.c. of air were blown in by pressure. The pulse-rate rose from 96 to 214 per minute. Tracings were taken at intervals over five hours, when the animal was killed. Post mortem the right lung was almost completely collapsed and airless, the pleural cavity being full of air. The left pleura contained 750 c.c. of blood, but the left lung was well aerated.

The changes in ventricular pressure were as follows:

	Systolic. mm.	Diastolic. mm.
Normal	21·5	5·5
1¼ hours after infusion of blood	23·5	11·0
½ hour after pneumothorax	44·5	28·0
1½ hours after pneumothorax	33·5	27·5
4¼ hours	similar	

In this instance the injection of air into the thorax under pressure caused a very great increase, not only in diastolic but also in systolic pressure. The result was the same as that produced by injection of a large quantity of blood. The great rise in systolic pressure showed that a considerable obstruction was imposed on the circulation through the pulmonary arteries.

The work embodied in this communication was carried out at the suggestion of Mr. Joseph Barcroft, F.R.S., and under his direction. The writer has to express to him most cordial thanks for helpful advice and criticism.

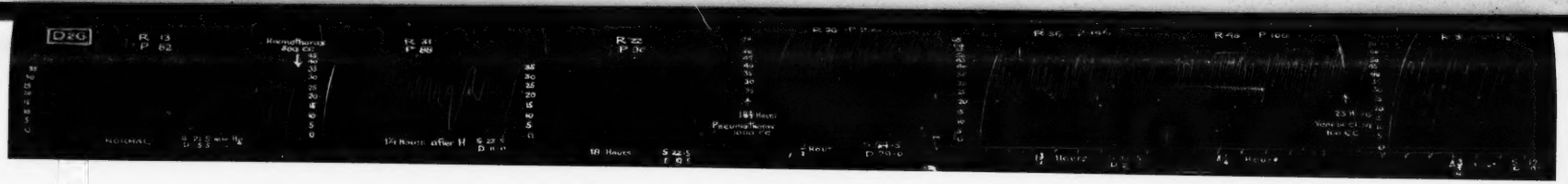

FIG. 1

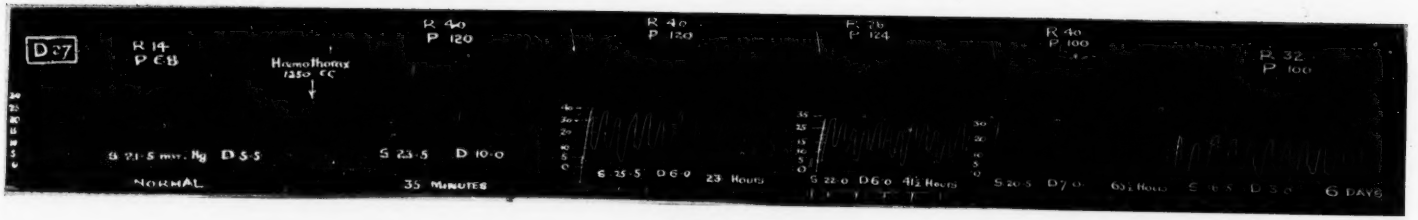

FIG. 2

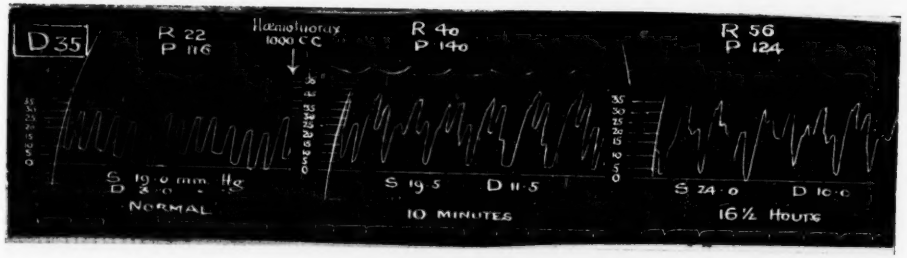

FIG. 3

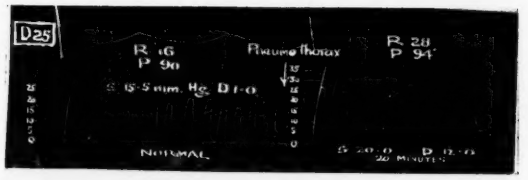

FIG. 5

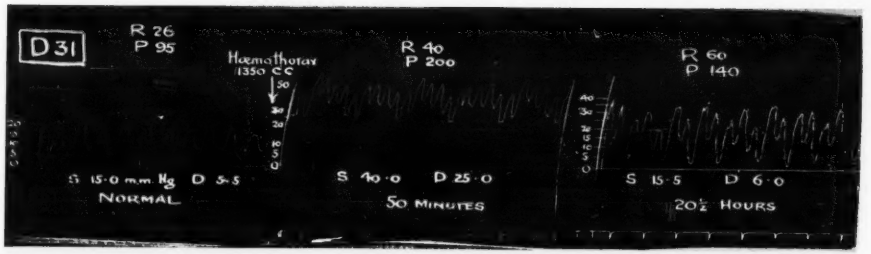

FIG. 4

THE INFLUENCE OF DIGITALIS ON THE DIFFERENT PHASES OF THE HEART-BEAT, PARTICULARLY AS REGARDS THE INTRACARDIAC PRESSURE

By I. HARRIS

(From the Cardio-Therapeutic Department, David Lewis Northern Hospital)

With Plates 2 and 3

In this paper an attempt is made to study the influence of digitalis on the different phases of the heart-beat, particularly as regards the intracardiac pressure. There is no need for me to enter into the controversy as to whether digitalis acts directly on the heart-muscle or on the inhibitory apparatus. It is necessary, however, in order to appreciate fully the effect of digitalis on the human heart, to keep before one's mind one or two simple facts culled from experimental pharmacology.[1]

There is hardly any doubt that experiments on animals have demonstrated that digitalis has a double action, with effects which are more or less opposed to each other.

In so far as it acts on the inhibitory apparatus, it prolongs both diastole and systole, and the heart output is actually diminished; while its direct action on the cardiac muscle shortens both systole and diastole. The contraction of the heart becomes more powerful and the output of the ventricle greater.

The method employed in this observation consists simply in the taking of an electro-cardiogram before and after the administration of digitalis. The drug was administered *per os* in the form of tincture. The observation was made chiefly on out-patients, and also on a number of in-lying cases.

The ventricular systole was determined by the ventricular complex of the electro-cardiogram. According to Lewis (2) the earliest sign of contraction in the ventricle occurs in the commencement of R, and usually during the upstroke. In order to obtain a more stable point from which to begin the measurements, I have taken the junction where the horizontal line meets R or Q as the commencement of the systole, and the place where T passes into the horizontal line as the end of the systole. This slight disparity between the actual commencement of the

systole and the beginning of *R* is of no great consequence in measurements taken solely for purposes of comparison.

As regards the influence of digitalis on the pulse frequency, three distinct stages are discernible. 1. Digitalis diminishes considerably the pulse-rate. 2. The pulse-rate remains about the same as before the administration of the drug. 3. Digitalis greatly accelerates the pulse frequency. A typical action of digitalis on the human heart, if the drug is continued for long, is to start with stage 1, pass through stage 2, and finally end in stage 3.

While the retarding effect of digitalis on the pulse is not constant, it invariably accelerates the pulse provided that a sufficient quantity of digitalis is given long enough. It depends on the condition of the heart-muscle what amount of digitalis is necessary to effect a translation of the heart from stage 2 to stage 3. Case No. 3, a case of chronic myocarditis, has reacted to 5 minims of digitalis thrice daily for a week by a considerable fall of the pulse-rate. The continuation of larger doses of digitalis for another week had the effect of greatly accelerating the beat. In other cases a large dose of digitalis may be given for many weeks without producing a great acceleration in the pulse-rate.

The effect of digitalis on different phases of the heart-beat is variable and depends to a large extent on the pulse-rate. There is no necessity for me to deal with the auricular phase, which has already received an exhaustive treatment from many observers. The systole is remarkable for its stability so far as length is concerned. Whatever the condition of the cardiac action may be, there is very little difference in the duration of the systole in different individuals. I have examined some hundreds of cardiograms, and if we except heart-failure, gross lesions of the myocardium, and the influence of drugs, the duration in almost all cases varies between 0·32 and 0·36 of a second. As a rule, it is nearer the first figure than the second. Very rarely it is below the first, in very few cases it exceeds the second figure. In stage 1 the systole is prolonged, although not to the same extent as the diastole (about $\frac{1}{2\cdot5}$ of a second is a good average). In the second stage the systole is actually shorter than before the administration of digitalis, although the pulse-rate remains the same, and even when it is lessened. This is easier to demonstrate in cases where the duration of the systole before the administration of digitalis is relatively long.

In the third stage arising under the influence of digitalis the duration of the systole is still shorter. This shortening exceeds considerably the lower limit of variation found under normal circumstances in the human heart, and in the first two stages. The systole is shorter by more than one-half than it is prior to giving digitalis.

The diastole in the first stage is greatly, in the second stage slightly, increased, and in the third stage may become diminished to such an extent as to be actually shorter than the systole. Whilst thus the relative length of the diastole as compared with the systole is longer in stages 1 and 2 under digitalis, we find it may be actually shorter than the systole in the third stage.

Other Changes in the Electro-cardiogram produced by Digitalis.

There is no need to refer to the *PR* interval, to the coupled beats, and the different irregularities which are due to digitalis. These have been exhaustively dealt with by other writers. I will refer only to two alterations in the character of the electro-cardiogram which digitalis produces. The one is digitalis depression, the other is an alteration in the *T*-wave.

The digitalis depression has been described by me in a short note published in the *Lancet* (4). It is a curious depression in the electro-cardiograms between *R*[1] and *T*. In the average of my cases, one drachm of digitalis per diem has produced this phenomenon, although in one case the depression was already marked after five minims of digitalis thrice daily for a week. Here again it depends on the condition of the myocardium which doses are required to produce this phenomenon. In one case, just after acute rheumatism, 5 minims of digitalis thrice daily were sufficient to produce this phenomenon. A few months later, when the state of the patient's heart was considerably improved, it took 20 minims twice daily for two weeks to produce the same depression. The depression is more pronounced, and it takes a smaller quantity of digitalis to produce it, in old age. But an important fact in connexion with the depression is that I have never seen it in stage 1 under digitalis. It invariably makes its appearance either when the pulse-rate has not slowed down at all under the administration of digitalis, or when it has done so to a moderate extent only. I have never seen this depression where the heart is in the third stage. The depression remains noticeable till about three weeks after the discontinuance of the drug. Atropin has no influence on its duration. When the depression is marked the patient usually complains of difficulty in breathing, faintness, &c.

T-wave. Cohn (3) has already described an alteration of the *T*-wave under the influence of digitalis which takes the form of an inversion. I have seen this inversion only in lead 1, but the amplitude of *T* in lead 2 is considerably diminished.

Strophanthus. I have never seen any strong reaction in the heart produced by this drug. I have never been able to observe a similar depression in the electro-cardiograms taken from patients under the influence of strophanthus, no matter how large the doses were. I have but rarely seen an alteration in the *T*-wave as a consequence of strophanthus treatment. However, as I have been in the habit of administering strophanthus *per os*, the contention of Cushny, that strophanthus given *per os* in aqueous solution is ineffective, may account for the poor result obtained.

[1] It is suggested that a digitalis depression has something to do with inverted *T*. This is not so. Where *T* is inverted it is well defined in shape and form, and its occurrence as regards time is the same as in normal *T*. The contrary is true. Digitalis depression often affects the shape of *T*-wave, so that only the part of it which is not affected remains normal. Where the depression is not much developed, so that it does not become necessary for it to encroach on the space of *T*, its independence is manifest. In the same manner the depression may also affect the shape of *R*. Finally, inverted *T* and digitalis depression find their maximum development in different leads.

Helleborein. Unlike other observers, I noticed a great slowing of the pulse produced by administration of this drug. This result may possibly be due to the fact that I have prescribed helleborein in large doses (one drachm of the liquor three times a day). I have never seen digitalis depression as a result of an administration of the drug. I find caffeine prolongs the systole, and both caffeine and camphor increase considerably the amplitude of the *T*-wave.

Discussion.

One of the most important features of uncomplicated heart-failure is the greatly accelerated pulse. Such a pulse differs from the normal pulse in that the relative durations of systole and diastole have undergone a profound change.

The diastole is often actually shorter than the systole. Let us consider for a moment the mechanism of heart-failure. The heart-muscle is unable to stand the strain of intracardiac pressure and gives way by dilatation. The diastole of the dilated heart is shorter than the normal diastole. This shortening of its duration implies that a smaller quantity of blood reaches the heart than in the normal condition. The result is that at the beginning of the systole there is less blood in the ventricle and the ventricular pressure is proportionately lessened. Clearly, the acceleration in the pulse-rate in this case should be looked upon as an adaptation of the organ to special circumstances, failing which the heart would be unable to accomplish the necessary amount of work. As the output at each beat is smaller than normally, the number of contractions must increase. Even so, the increase in the pulse-rate finally fails to make up for the smaller quantity of blood given out at each contraction, with the result that venous engorgement takes place. This is the cardiac condition in which digitalis is usually indicated.

To simplify matters, we shall leave out of consideration the tonic and sedative qualities of digitalis on the heart. If digitalis would simply lengthen the diastole without affecting in any way the systole the intracardiac pressure would be even higher than normally. Such a drug would hardly be indicated under the circumstances. Let us now look at the nature of the action of digitalis in its first stages. We know from experiment on animals that when digitalis slows the pulse-rate it acts on the inhibitory apparatus. We have seen what such action means: it prolongs not only the diastole, but also the systole, though the latter to a smaller extent. The systolic contraction is less powerful than it is before the heart-failure occurs. True, the diastole is longer, but we have reason to believe that the flow of blood to the heart takes place at a slower rate than normally. In addition, the slowing of the pulse-rate gives the heart so much more time to recuperate. Thus, whereas the intracardiac pressure in the first stage of digitalis is less and certainly not higher than normally, the heart action takes place under more favourable conditions. In the second stage of digitalis the slowing of the pulse-rate diminishes, and may even reach normal level. We know from animal experiment that this means a direct action of digitalis on the heart-muscle, and that under these circumstances the systolic contraction is more

powerful and makes a greater demand on the heart-muscle. We have seen also that the systole is actually shorter than in the normal condition. This means that a normal quantity of blood is driven out under a greater intracardiac pressure. Thus the strain on the heart-muscle will be correspondingly greater. It is obvious also that the two diametrically opposed effects of digitalis might overbalance each other either way, not only when the pulse has reached the normal rate, but even before or after that. With the continued administration of digitalis its effect on the heart-muscle continues to increase. Then occurs what is usual whenever the heart-muscle is no longer able to stand the strain, viz. a great and sudden acceleration in the pulse-rate, the diastole becoming shorter than the systole. The ventricles contain only a relatively small quantity of blood at the time of contraction, with the result that the intracardiac pressure falls considerably. This is the third stage of digitalis action on the heart.

If the acceleration of the pulse-rate in these cases was due to the paralysis of the inhibitory apparatus, as is generally held to be the case, it would be difficult to understand why digitalis should so much more easily produce the acceleration of pulse in the myocardiac condition than in the normal heart.

So far as the digitalis depression is concerned, I regard it as a reaction of the heart, a response by dilatation to the rise of intracardiac pressure. This depression does not occur either in stage 1 or in stage 3: in short, where there is no rise in blood-pressure. This is also in conformity with the fact that usually the patient is feeling unwell and the depression is marked. The fact, too, that in the diseased heart-muscle digitalis produces it more easily indicates that the intracardiac pressure has something to do with it. We have also seen that it is produced more easily and is generally more marked in old age, a time of life, as a correspondent in the *Lancet* (5) pointed out, when the heart is little adaptable to variations of intracardiac pressure. In connexion with digitalis, if we survey all the facts gathered clinically and experimentally, we shall easily come to the conclusion that it is a dangerous drug, which may not be prescribed indiscriminately, a fact fully appreciated in former times, but frequently sinned against by modern cardiologists. Irregularity, increase in the *PR* interval, coupled beats, digitalis depression, inversion of *T*, are all pathological conditions which are doubtless harmful to the heart. Digitalis ought not to be pushed to such an extent as to produce these phenomena. Even in those cases where the digitalis treatment is most successful—in auricular fibrillation—it owes its effect to a quality which otherwise would not commend itself to us as a virtue. With few exceptions the administration of digitalis ought only to be continued as long as it produces an appreciable slowing of the pulse-rate.

I am indebted to the Medical Board of the Northern Hospital for permitting the use of material in connexion with this paper.

TABLE I.

A girl of seventeen. Mitral regurgitation—compensation good—only slight amount of hypertrophy of left ventricle. No evidence of myocardial trouble.

8.1.18.

Whole Pulse in Seconds.	*P–R.*	*R–T.*	*T.*	*P.*	Digitalis Depression.
0·94	0·16	0·35	L I. Inverted	L I. Inverted	L I. Nil
0·84	0·16	0·4			
0·78	0·16	0·36	L II. Slightly marked	L II. Normal	L II. Nil
0·82	0·16	0·36			
0·72	0·16	0·36			
0·74	0·16	0·4	L III. Well marked	L III. Normal	L III. Nil
0·86	0·16	0·36			

The whole pulse is taken from *R* to *R*.

15.1.18. Since 8.1.18 Digitalis ℞ xx thrice daily (t. d. s.).

0·72	0·16	0·32	L I. Inverted	L I. Inverted	L I. Absent
0·70	0·16	0·32	L II. Well marked	L II. Normal	L II. Fairly marked
0·86	0·2	0·32			
0·76	0·16	0·32	L III. Well marked	L III. Normal	L III. Fairly marked

22.1.18. Since 15.1.18 Digitalis ℞ xxv thrice daily (t. d. s.).

0·92	0·2	0·34	L I. Inverted	L I. Inverted	L I. Absent
0·84	0·2	0·32			
0·96	0·2	0·32	L II. Not inverted, but badly developed	L II. Normal	L II. Well marked
0·80	0·21	0·34			
1·24	0·2	0·36	L III. Present	L III. Normal	L III. Marked

5.2.18. Since 22.1.18 Digitalis ℞ xxv t. d. s.
Since 29.1.18 Helleborein.

1·14	0·22	0·34	L I. Inverted	L I. Inverted	L I. Absent
1·14	0·2	0·36			
1·23	0·22	0·35	L II. Normal	L II. Normal	L II. Slightly marked
1·16	0·2	0·36			
1·12	0·2	0·36	L III. Normal	L III. Normal	L III. Present

19.3.18. Since 12.3.18 Helleborein.

0·78	0·22	0·34			
1·20	0·22	0·32			
1·08	0·2	0·36			

TABLE II.

Robinson. Male, aged 52. A medium degree of arteriosclerosis of vessels and heart—is able to do a normal day's work.

2.10.17.

Whole Pulse in Seconds.	*P–R.*	*R–T.*	*T.*	*P.*	Digitalis Depression.
0·7	0·2	0·35	L I. Marked	L I. Normal	L I. Nil
0·68	0·2	0·34			
0·68	0·2	0·34	L II. Marked	L II. Normal	L II. Nil
0·7	0·2	0·32			
0·7	0·2	0·32	L III. Marked	L III. Normal	L III. Nil
0·68	0·2	0·34			
0·68	0·22	0·34			
0·66	0·2	0·32			

9.10.17. Digitalis (1) x t. d. s. since 2.10.17.

0·70	0·2	0·35	L I. Marked	L I. Inverted	L I. Nil
0·70	0·2	0·36			
0·74	0·24	0·36	L II. Marked	L II. Marked	L II. Nil
0·74	0·2	0·34			
0·70	0·22	0·36	L III. Marked	L III. Marked	L III. Nil
0·82	0·2	0·34			
0·82	0·2	0·36			
0·74	0·2	0·36			

16.10.17. Digitalis (1) xv t. d. s. since 9.10.17.

0·82	0·24	0·33	L I. Marked	L I. Not developed	L I. Well marked
0·80	0·24	0·33			
0·78	0·24	0·33			
0·80	0·24	0·35	L II. Marked	L II. Normal	L II. Well marked
0·80	0·24	0·36			
0·80	0·24	0·35	L III. Marked	L III. Normal	L III. Not present

6.11.17. Digitalis (1) xx t. d. s. since 16.10.17.

0·72	0·24	0·32	L I. Very slight	L I. Inverted	L I. Very marked
0·70	0·24	0·32			
0·69	0·24	0·28			
0·71	0·24	0·32	L II. Very slight	L II. Normal	L II. Very marked
0·71	0·24	0·32			
0·71	0·24	0·32			
0·68	0·24	0·32	L III. Very slight	L HI. Normal	L III. Not marked
0·70	0·24	0·32			
0·67	0·24	0·32			
0·64	0·24	0·3			
0·64	0·24	0·3			

TABLE III.

Mann. Male, aged 40. Chronic myocarditis – can do but little work.

26.3.18.

Whole Pulse in Seconds.	*P–R.*	*R–T.*	*T.*	*P.*	Digitalis Depression.
0·64	0·2	0·32	L I. Inverted	L I. Normal	L I. Nil
0·65	0·2	0·32	L II. Marked	L II. Normal	L II. Nil
0·66	0·2		L III. Marked	L III. Normal	L III. Nil
			2.4.18. Digitalis (α) v t. d. s. since 26.3.18.		
0·8	0·2	0·32	L I. Normal	L I. Normal	L I. Nil
0·78	0·2	0·33			
0·76	0·2	0·32	L II. Well developed	L II. Normal	L II. Nil
0·85	0·2	0·32			
0·74	0·2	0·36			
0·70	0·2	0·36	L III. Well developed	L III. Normal	L III. Nil
0·72	0·2	0·32			
			9.4.18. Digitalis (α) x t. d. s. since 2.4.18.		
0·34	0·14	0·12	L I. Marked	L I. Marked	L I. Nil
0·27	0·1	0·16	L II. Marked	L II. Marked	L II. Nil
0·38	0·1	0·143	L III. Marked	L III. Marked	L III. Nil

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2. Lewis, *Electro-cardiography*, Lond., 1912.
3. Cohn, *XVIIth International Congress of Medicine*, Lond., 1913, Sect. VI, Med. Pt. II. 257.
4. Harris, *Lancet*, Lond., 1916, i.
5. *Lancet*, Lond., 1914, i. 910.

EXPLANATION OF FIGURES.

PLATE 2, FIGS. 1 and 2, and PLATE 3, FIG. 3 show the gradual development of the digitalis depression.

FIG. 1 was taken before the administration of the digitalis.

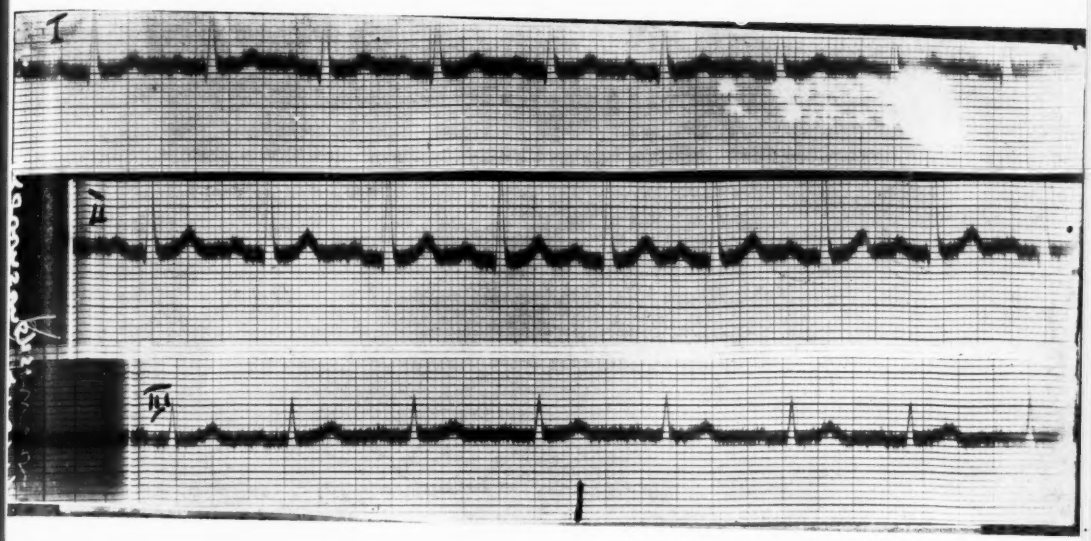
FIGS. 2 and 3 after the administration of the digitalis.

FIGS. 4, 5, and 6 show the influence of digitalis under different phases of the heart-beat.

FIG. 4. Before the administration of digitalis.

FIG. 5. The same patient after digitalis.

FIG. 6 is a typical cardiogram, or the third stage of digitalis.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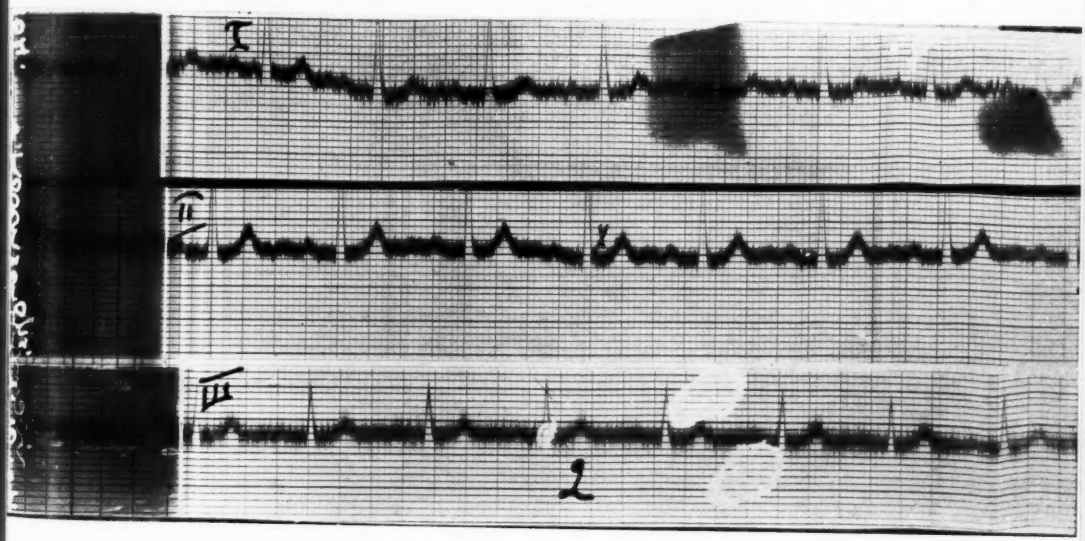
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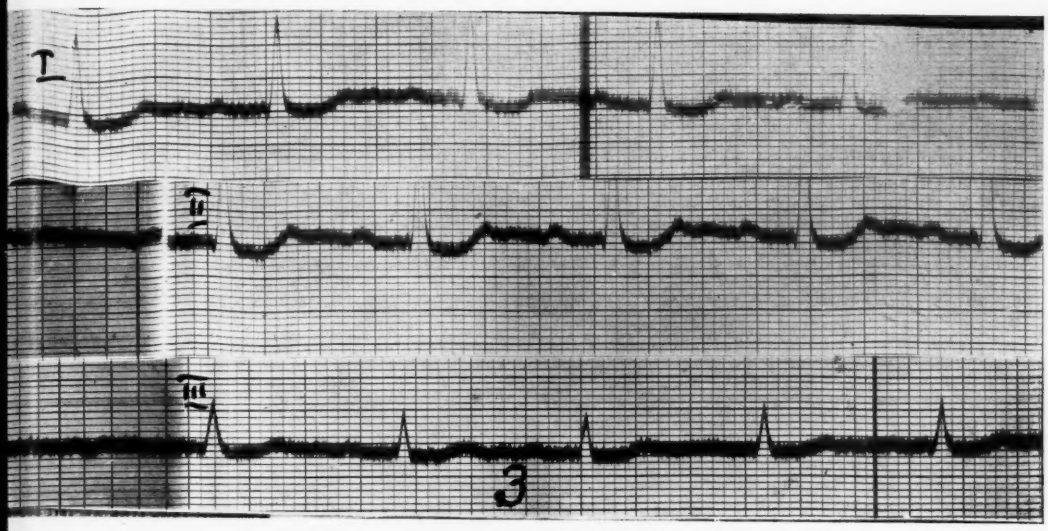
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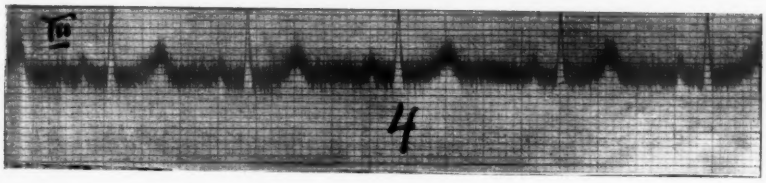
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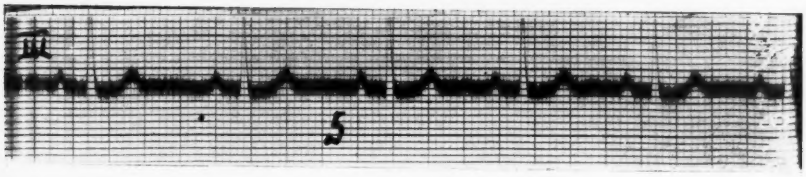
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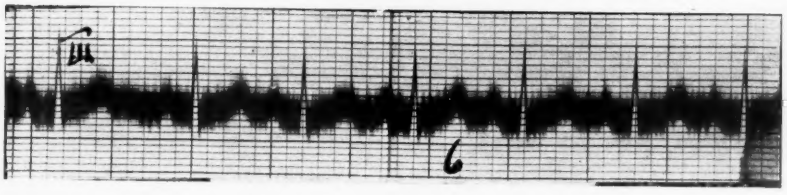

III
6

PRIMARY PULMONARY TUBERCULOSIS IN CHILDREN[1]

By R. G. CANTI

(From the Pathological Laboratory, St. Bartholomew's Hospital)

In 1916 Barty King (1) published a translation of A. Ghon's *Die primare Lungenherd bei der Tuberkulose der Kinder.*

Kuss, E. Albrecht, H. Albrecht, Ghon, and others belong to a school which holds that there is a special form of tuberculosis in children, consisting of a primary lung focus, caused by inhalation of tubercle bacilli. This focus is responsible for the greater number of deaths from tuberculosis in children, and, as a rule, escapes clinical diagnosis.

Ghon performed autopsies on 644 cases, of which 184 (28·57 per cent.) were tuberculous, and of these 170 (92·40 per cent.) showed what he believes to be, a primary focus of infection in the lung.

The present work was undertaken with a view to repeating these observations. The cases dealt with form a continuous series of eighty-four autopsies in children up to 10 years of age, carried out by the writer at St. Bartholomew's Hospital. The series is not entirely free from involuntary selection, owing to the presence of an abnormally large proportion of children under one year of age (thirty-three cases or 39·30 per cent.), and the absence of cases of bone and joint disease, most of which find their way to special hospitals.

According to Ghon the lung focus is usually small, and varies from the size of a pin's head to that of a cherry; most often it is about the size of a pea. It is usually single (72·35 per cent.), and only on rare occasions are more than two or three foci found. The focus is presumed to have origin in the aggregations of lymphoid tissue found in the neighbourhood of the small bronchi, the evidence brought forward in support of this view being that a fissure, which is thought to be the remains of a small bronchus, is frequently found in the middle of a focus, and further, that on tracing distally along a bronchus a dead end is frequently reached which is found to be within a focus, and that the tissue beyond such a focus is oftentimes atelectatic.

The focus, commencing as a small tubercle, soon increases in size and involves

[1] This work was carried out under the auspices of the Medical Research Committee, from whom a grant was received.

the neighbouring structures. Around it small anatomical tubercles may frequently be seen, and fibrous tissue may be formed in an attempt at encapsulation. In the larger foci caseation usually takes place, which is hard and dry rather than soft or liquid, but occasionally a cavity is formed. The process may be arrested during any of these stages, as evidenced by fibrosis or calcification.

The situation of the focus is usually immediately beneath the pleura, which is frequently involved. The right lung is more often affected than the left (3 : 2), and the order of frequency with which the various lobes are involved, in cases where only one lung focus is found, is as follows :

Right upper lobe	30·98 per cent.
Left upper lobe	23·24 „ „
Right lower lobe	22·54 „ „
Left lower lobe	15·49 „ „
Right middle lobe	7·75 „ „

Kuss, however, states that the lower lobes are more frequently affected than the upper.

Lesions are scarcely ever found at the apices, the commonest site in the upper lobes being the middle of the anterior surface. In the lower lobes the posterior surface near the lower edge is most frequently affected.

The mediastinal glands are classified by Ghon in four groups :

Superior tracheo-bronchial . .	Those in the angle between the trachea and bronchus on either side.
Inferior tracheo-bronchial . .	Those in the bifurcation of the trachea.
Paratracheal	Those forming a chain on either side of the trachea.
Broncho-pulmonary	Those at the hilus of the lung and between the branches of the main bronchi.

From anatomical observations it has been found that the superficial and deep lymphatic vessels discharge their contents, first into the broncho-pulmonary glands, and then into one of the remaining groups, which are closely connected together by anastomosing lymphatic vessels. For the most part the lymphatic vessels from the middle and lower portions of the lung discharge their contents into the inferior tracheo-bronchial glands, and those from the upper lobes into the superior tracheo-bronchial glands, whence crossing over the middle line frequently takes place.

Two facts of importance are found with regard to the relation of the lung focus to the mediastinal glands; the first is that if there is a lung focus there are also tuberculous glands in the mediastinum (Ghon has reported one case in 170 in which this was not so); the second is that if the glands are affected a tuberculous focus in the lung is present (Ghon has reported seven cases showing

tuberculosis of the glands of the mediastinum with no evidence of a source of infection outside the lung, in which he was unable to find a lung focus).

The glands exhibit the familiar lesions of tuberculous lymphatic glands. If their apparent age be compared with that of the lung focus it is found that either the lung focus is older or of the same age. It never appears more recent.

With regard to the relation between the glands and the lung focus it is found that the infection of the glands follows the course which might be expected from a knowledge of the anatomical arrangement of the mediastinal lymphatic system. A focus, for example, in the right upper lobe will be found to be accompanied by lesions in the broncho-pulmonary glands, especially those in relation to the eparterial bronchus. These lesions will not be extensive, as the initial size of the glands is not great. The infection, having passed this barrier, will reach the groups of glands in relation to the main bronchus and the trachea. Of these groups the right superior tracheo-bronchial will be the first and the most severely affected. Owing to intimate anastomosis the infection may spread to neighbouring groups, first to the right paratracheal and the inferior tracheo-bronchial, and later to the left superior tracheo-bronchial group. In like manner a lesion in any other situation in the lung will be found to be accompanied by a similar spreading out of the glands in the form of a fan or segment of a circle, the focus being found at the handle of the fan, or centre of the circle.

Thus, if the distribution of affected lymphatic glands in the mediastinum be examined, it is usually possible to predict with certainty the situation of the lung focus, and, as a rule, no difficulty is experienced in detecting the focus within a few seconds by palpating and sectioning the suspected lobe.

As the disease progresses fresh lesions occur, which must be carefully distinguished from the original focus. Important amongst these are tuberculous broncho-pneumonia, due to discharge of material from the focus or perforation of a bronchus by an adherent gland; the adhesion of a gland to the lung tissue and the resulting spread of the lesion by direct extension; and a haematogenous infection resulting in miliary tuberculosis with or without broncho-pneumonia.

In order to establish the priority of the lung focus it is necessary to show, first, that it is older than the lesions in the mediastinal glands, and, secondly, that it is older than any other focus which may be present in the body.

It is held by many that the disease is primary in the mediastinal glands, the reason put forward being either that the glandular tuberculosis is the only disease seen at autopsy, or that, if a focus is present in the lung, it is much smaller than the affected glands, and therefore secondary to them.

Against these arguments Ghon puts forward the following:

(1) On studying the distribution of affected glands it is found, from a knowledge of the anatomy of the lymphatic system of the lungs and mediastinum, that those glands are tuberculous which one would expect to find tuberculous if the lung focus were primary.

(2) The changes in the glands always appear of more recent date than, or at least only of the same age as, the lung focus. They never appear older.

(3) Tuberculous glands in the mediastinum are hardly ever found without a corresponding lesion in the lung.

The hypothesis of a primary lung focus becomes even more tenable if the propagation of the disease in the reverse direction be considered. If this unlikely theory be correct, the disease, having commenced and spread in the mediastinal glands, must arbitrarily have selected a point in the lung more or less remote from the infected glands for the deposition of a single secondary focus, leaving the intervening lung tissue free from tuberculosis.

Again, the argument that the lung focus is not primary because it is smaller than the gland lesion does not hold good, for it must be remembered that glands are organs designed to hypertrophy to many times their normal size in order to cope with infection, whereas no such mechanism is present in other tissues, where the reaction is local, and is set up for the purpose of limiting or reducing the size of the lesion.

As a preliminary step in proving that the disease may reach the lung by metastasis from some other focus in the body, it would be necessary first to establish the presence of such a focus, and, secondly, to demonstrate that it is older than the focus in the lung. But Ghon has shown that only in 8·87 per cent. of cases could a focus elsewhere be shown to be of the same age as the lung focus, and in no case was there evidence that it was of greater age. Further, in a disease of the nature of tuberculosis, it would be expected that metastases would be multiple in a large proportion of cases, whereas in his series 72·35 per cent. of the cases showed only one lung focus.

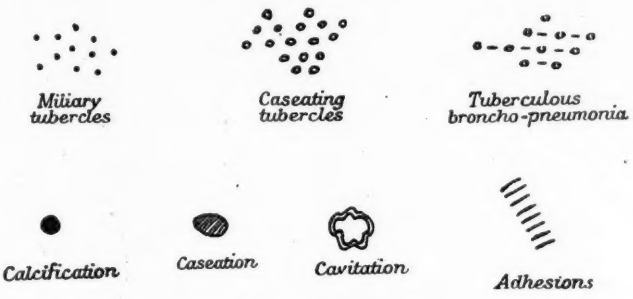
The question as to the channel of infection of thoracic tuberculosis in children has been investigated from quite a different point of view by Eastwood, F. Griffith, and A. S. Griffith, who studied the types of tubercle bacilli found in various lesions. Bearing in mind that an air-borne infection is derived almost entirely from the sputum of phthisical patients, and that these are infected for the most part with the human type of tubercle bacillus, and that ingestion tuberculosis is derived almost entirely from milk infected with the bovine type of bacillus, it is reasonable to suppose that if the organism in thoracic tuberculosis in children were due to inhalation the human type of bacillus would be present, and that if the thoracic lesion were metastatic the organism isolated would be of the type most commonly found in connexion with intestinal lesions.

After selecting cases where there was strong anatomical evidence in favour of the lesion having arisen in the respiratory tract, Eastwood and F. Griffith (2) found forty-three cases yield the human type of tubercle bacillus out of forty-four cases from which tubercle bacilli were cultivated, and A. S. Griffith (2) found all of twenty-two cases yield the human type of tubercle bacillus. When, however, cases were selected where there was strong anatomical evidence that the infection was alimentary in origin, Eastwood and F. Griffith found that twelve out of fifteen cases, and A. S. Griffith six out of eight cases, yielded the bovine type of tubercle bacillus.

In the present series of eighty-four cases, sixteen (19·05 per cent.) showed

tuberculous lesions. The following are short notes of these cases, together with diagrams, compiled from dissection of the thoracic contents:

I. *Cases showing Foci in the Lungs.*



KEY TO DIAGRAMS.

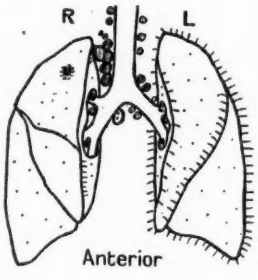


FIG. 1.

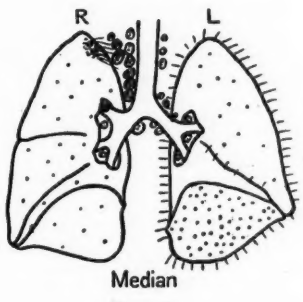


FIG. 2.

Case I. Figs. 1 and 2. Male, aged 6 years. Cause of death: tuberculous meningitis.

A liquefying caseous focus the size of a large pea, surrounded by a zone of large tubercles and situated immediately beneath the middle of the anterior surface of the right upper lobe. Two or three small fibro-caseous foci surrounded by confluent tubercles situated at the right apex. Large miliary tubercles in moderate numbers throughout the lung, especially on the diaphragmatic surface of the left side. Adhesions all over the left pleura and mediastinal surface of the right middle lobe. Adhesions between right apex and neighbouring glands. A few small right paratracheal glands, the lower ones caseous and the upper showing anatomical tubercles. A chain of small left paratracheal glands showing small tubercles. Mass of about four caseous right superior tracheo-bronchial glands, the largest the size of a cob-nut. A few small caseous left superior tracheo-bronchial glands with anatomical tubercles, the largest on the right side. One small caseous gland in relation to the eparterial bronchus, and several other small broncho-pulmonary glands on either side, showing miliary tubercles. Generalized tuberculosis, tuberculous meningitis.

Case II. Fig. 3. Female, aged 7 years. Cause of death: tuberculous meningitis.

Calcareous focus, the size of a hemp-seed, situated in the middle of lower anterior edge of the right upper lobe. Adhesions all over the right side. One

caseous right paratracheal gland the size of a cob-nut, one small caseous right superior tracheo-bronchial gland the size of a small pea, one small caseous broncho-pulmonary gland below the eparterial bronchus. Caseous tuberculoma of the cerebellum, tuberculous meningitis. One small calcareous tubercle of spleen.

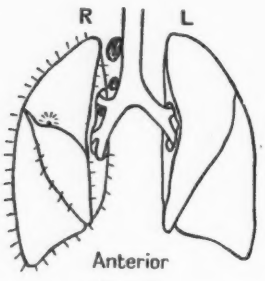


FIG. 3.

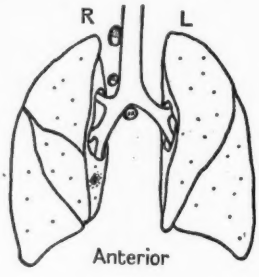


FIG. 4.

Case III. Fig. 4. Female, aged 6 years. Cause of death: tuberculous meningitis.

Focus the size and shape of half a split pea, consisting of a mass of confluent caseous tubercles situated on the mediastinal surface of the right middle lobe and involving the pleura. Moderate sprinkling of grey miliary tubercles throughout both lungs. One semi-caseous right paratracheal gland the size of a large cob-nut. One small partly caseous right superior tracheo-bronchial gland. One small inferior tracheo-bronchial gland, with miliary tubercles, situated in the middle line. A few fair-sized caseous tubercles of kidney. A few miliary tubercles in liver.

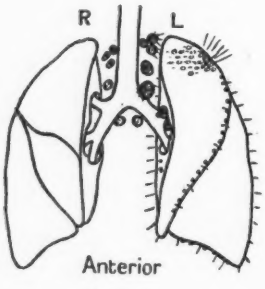


FIG. 5.

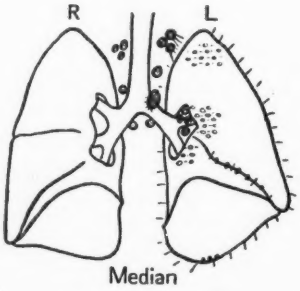


FIG. 6.

Case IV. Figs. 5 and 6. Female, aged 4½ years. Cause of death: tuberculous meningitis.

Caseating focus, the size of a large cob-nut, situated in the left upper lobe somewhat anterior to the mid-axillary line, one inch below the apex, and involving the pleura between the lobes as well as on the surface of the lung. Large miliary tubercles and tuberculous broncho-pneumonia involving the upper portion of the left upper lobe, except at the extreme apex. Large miliary tubercles and tuberculous broncho-pneumonia at the root of the left lung. Adhesions all over left pleura. Large miliary tubercles in pleura, especially between the lobes, at the anterior edge of the lung, and on surface opposed to pericardium. Many caseous left paratracheal glands, the largest the size of an almond, some adherent to the apex. Many medium-sized semi-caseous right paratracheal glands. Large caseous right superior tracheo-bronchial gland firmly adherent to bronchus. Medium-sized left superior tracheo-bronchial gland with

anatomical tubercles. Two small inferior tracheo-bronchial glands with anatomical tubercles. Several small caseous left broncho-pulmonary glands situated about the superior bronchus. Tuberculous meningitis. Large tubercles of spleen, diaphragm, and pericardium.

Case V. Fig. 7. Female, aged 1½ years. Cause of death: tuberculous meningitis.

A caseous focus, the size of a large pea, situated on the inner surface of the left upper lobe a short distance below the apex, with a few large miliary tubercles in the neighbourhood. Tuberculous broncho-pneumonia of the upper portion of left upper lobe. Scanty miliary tubercles throughout both lungs. Adhesions between upper and lower lobes on the left side and upper and middle lobes of right side. Many moderate-sized caseous left paratracheal glands. A few small caseous right paratracheal glands. A large group of moderate-sized caseous left superior tracheo-bronchial glands surrounding the aorta and adherent to the lung. One small caseous inferior tracheo-bronchial gland on either side. Several medium-sized caseous left broncho-pulmonary glands. Generalized tuberculosis, tuberculous meningitis.

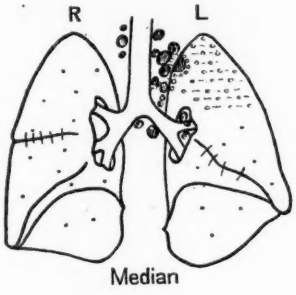


FIG. 7.

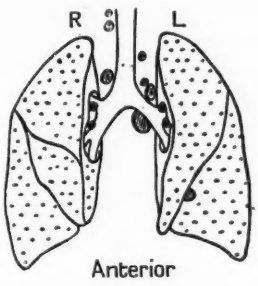


FIG. 8.

Case VI. Fig. 8. Female, aged 6 months. Cause of death: tuberculous meningitis.

A caseous focus, the size of a large pea, situated on the interlobar edge of the left lower lobe in front. Large miliary tubercles, in many places confluent, throughout both lungs. Two right paratracheal glands the size of large peas, one caseous, the other showing anatomical tubercles. One caseous left paratracheal gland. One caseous right superior tracheo-bronchial gland, the size of a cob-nut. Two smaller left superior tracheo-bronchial glands. One liquefying inferior tracheo-bronchial gland, the size of a large cob-nut, more inclined to the left side than the right. A few small tuberculous ulcers, involving, but not exceeding, Peyer's patches, situated about the middle of the small intestine. Caseous mesenteric glands of the average size of a large pea. Generalized tuberculosis, tuberculous meningitis.

Case VII. Fig. 9. Female, aged 7½ years. Cause of death: tuberculous meningitis.

A caseous focus, the size of a large pea, surrounded by small tubercles, about 1½ inches above the lower posterior border of the left lower lobe and adherent to the pleura. A few scattered miliary tubercles throughout. A few small left paratracheal glands showing tubercles, of which some are confluent and caseous. Caseous left superior tracheo-bronchial gland, the size of a raisin. Many caseous inferior tracheo-bronchial glands, the largest the size of a raisin, and situated on the left side. Several left broncho-pulmonary glands with confluent caseous tubercles. Tuberculous meningitis.

Case VIII. Fig. 10. Male, aged 1½ years. Cause of death: meningococcal meningitis.

A fibro-caseating focus, the size of a cherry, situated about the middle of the diaphragmatic surface of the left lower lobe. Adhesion to the diaphragm over the region of the lung focus. A few caseating left superior tracheo-bronchial glands, the largest as big as an orange pip. Two caseous inferior tracheo-bronchial glands situated on the left side, the largest the size of a cob-nut. A large crop of discrete left broncho-pulmonary glands occupying a space the size of a walnut. None of these glands was larger than a large pea. Their cut surface showed confluent tubercles. A few small miliary tubercles of the liver and spleen.

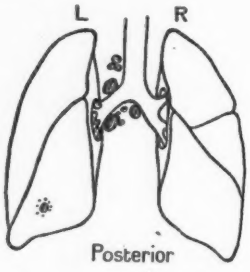


FIG. 9.

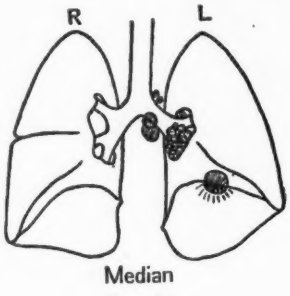


FIG. 10.

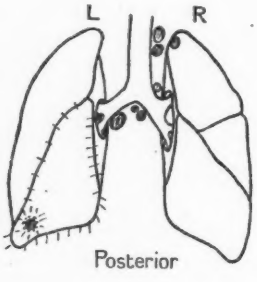


FIG. 11.

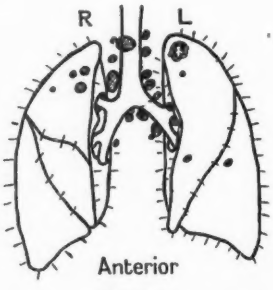


FIG. 12.

Case IX. Fig. 11. Female, aged 2½ years. Cause of death: tuberculous meningitis.

A caseous focus, the size of a pea, with tubercles surrounding, situated near the inferior edge of the left lower lobe behind and involving the pleura. Adhesions all over the external and interlobar surfaces of the left lower lobe. A caseous focus on the inner side of the right apex. Two large caseous right paratracheal glands. One small caseous right superior tracheo-bronchial gland. A few small caseous inferior tracheo-bronchial glands situated near the middle line, and one large gland situated on the left side, adherent to the left bronchus. One moderate-sized caseous left broncho-pulmonary gland between the main branches of the bronchus. Enlarged glands in the right side of the neck. Generalized tuberculosis, tuberculous meningitis.

Case X. Fig. 12. Male, aged 4½ years. Cause of death: tuberculous cachexia.

Cavity the size of a small cob-nut, irregular in shape, lining shaggy, surrounded with fibrous tissue, situated about the middle of the left apex. Two other foci, small and caseous, present in upper left lobe. One small caseous focus in lower left lobe in front near superior edge. Four foci, varying from the size of a hemp-

seed to that of a pea, the three largest caseous, present in the upper portion of the right upper lobe, three in front and three behind. All foci near the surface of the lung. Firm adhesions all over both lungs and between their lobes. Several caseous right paratracheal glands, the largest the size of a small cob-nut, lying somewhat in front of the trachea. Chain of small caseous left paratracheal glands. One caseous right superior tracheo-bronchial gland the size of a large cob-nut. Several small caseous left superior tracheo-bronchial glands. Several caseous inferior tracheo-bronchial glands, the largest, the size of a cherry, being on the left side. A few small caseous broncho-pulmonary glands on either side. Enlarged glands in neck, axillae, and groins. Tuberculous ulceration of colon. Numerous caseating mesenteric glands. Tuberculous focus in the left kidney the size of a hemp-seed. A few small anatomical tubercles in liver.

II. *Cases showing no Lung Foci (exclusive of Miliary Tuberculosis).*

Case XI. Fig. 13. Female, aged 7 years. Cause of death: purpura with jaundice.

Pleural adhesions at left apex, and at right base in the mid-axillary line. One left paratracheal and one left superior tracheo-bronchial gland, both fibro-caseous. Several caseous mesenteric glands.

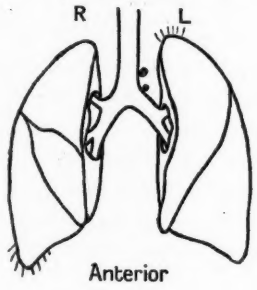


FIG. 13.

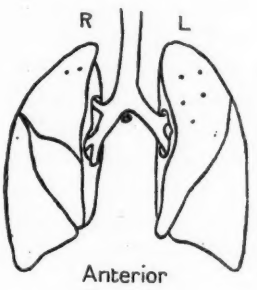


FIG. 14.

Case XII. Fig. 14. Female, aged 3 months. Cause of death: tuberculous meningitis.

Large, but scanty, miliary tubercles on surface of, and throughout, both upper lobes, one or two in left lower lobe. Small caseous inferior tracheo-bronchial gland in the middle line. Tuberculous peritonitis with considerable matting of intestines. Caseous mesenteric glands.

Case XIII. Male, aged 4 years. Cause of death: generalized tuberculosis.

Large and closely-set miliary tubercles throughout both lungs. Broncho-pulmonary and mediastinal glands enlarged and containing miliary tubercles. Two tuberculous ulcers in ileum. Tuberculous peritonitis. Matted mass of fibro-caseous mesenteric glands as big as fist. Generalized tuberculosis.

Case XIV. Male, aged 9 years. Cause of death: tuberculous peritonitis. Fair number of tubercles on visceral pleurae. Tuberculous peritonitis, with large numbers of tubercles over the peritoneum, and much adhesion. Moderate numbers of caseous mesenteric glands.

Case XV. Male, aged 6½ years. Cause of death: lymphatic leukaemia.

A few caseous mesenteric glands.

Case XVI. Female, aged 10 weeks. Cause of death: 'marasmus.'

Small anatomical tubercles, in large numbers, in mucous membrane of colon. (These were shown to contain giant cell systems and tubercle bacilli.)

The lung focus in this series was found to be most often the size of a pea. In one (Case II) it was small and difficult to find. The largest focus found was the size of a cherry, and occurred in a case (Case VIII) which died from meningococcal meningitis.

Single lung foci were found on eight occasions (Cases I–VIII). Two foci, apparently about the same age, were found in one (Case IX), and one (Case X) showed more than two foci, of which one, being cavernous, appeared decidedly older than the remainder.

In the majority of cases the focus was caseous or fibro-caseous. In one (Case II) it was calcareous, in one (Case I) liquefying, and in one (Case X) there was cavitation.

In all cases the lung focus was situated just beneath or involving the pleura. In the cases where only one lung focus was present it was situated in the left lower lobe in three cases, in the right upper lobe in two, in the left upper lobe in two, and in the right middle lobe in one.

Tuberculosis of the mediastinal glands, other than acute miliary tuberculosis, was found in twelve cases. In ten cases these glands were in anatomical relation to a lung focus in the manner already described, and in two (Cases XI and XII) no lung focus could be found. In each of these two cases the lesions in the glands were of small extent, and extensive abdominal tuberculosis was present. In all cases the most severely affected glands were caseous or fibro-caseous.

Tuberculous lesions of the intestines were found in four cases. In two (Cases VI and XIII) there was ulceration of Peyer's patches; in one (Case X) there was extensive ulceration of the colon; and in one (Case XVI) there were numerous small anatomical tubercles situated in the mucous membrane of the colon.

Tuberculous mesenteric glands were present in seven cases. They were present in three of the cases where tuberculosis of the intestines was found (Cases VI, X, and XIII), and in four cases in which neither tuberculosis of the intestine nor of the lung could be discovered.

In reviewing these cases as a whole it is found that ten (62·50 per cent. of all cases of tuberculosis) showed foci in the lung, and of these eight (80 per cent.) showed only one focus. Seven of these ten cases with lung foci showed no tuberculous lesions outside the thorax; three (Cases VI, IX, and X) showed lesions in or connexion with the alimentary tract. Of the remaining six cases in which no lung focus was found all showed abdominal tuberculosis.[1]

Broncho-pneumonic changes in the lung tissue, due apparently to the direct spread from a tuberculous lesion, were found in three cases. One (Case V) showed the change in the immediate neighbourhood of the lung focus; one (Case I) showed broncho-pneumonia with small foci of caseation, at the apex and in direct relation to an adherent tuberculous paratracheal gland; and one (Case IV, Fig. 6) showed tuberculous broncho-pneumonia both at the hilus,

[1] It is noteworthy that this series contains a larger proportion of cases of abdominal tuberculosis than reported by Ghon.

spreading apparently from the broncho-pulmonary glands, and at the apex, in the neighbourhood of the lung focus.

Miliary tuberculosis was found in five cases where a lung focus was present, and in two cases where no lung focus could be found.

From the foregoing it would therefore appear highly probable that tuberculosis of the mediastinal glands is secondary to a focus in the lung, and, further, that the focus in the lung is primary and not secondary to a focus elsewhere. For if the incidence of the primary lung focus be not accepted we are faced with the following anomaly, namely, that if the lung focus is metastatic, then it is at least curious that cases with a lung focus usually show no other evidence of a possible portal of entry, and, conversely, that where there is evidence that tubercle bacilli may have entered through some other organ, then it is uncommon to find a lung focus. If this anomaly be admitted there remains the argument that a lung focus is a metastasis from a focus elsewhere, and that only when this focus is undiscoverable does a metastasis in the lung occur. And this is manifestly absurd.

Conclusion.

The findings in this series agree substantially with those of Ghon. Any differences which may exist are numerical rather than qualitative, and are no greater than might reasonably be expected considering the difference of the conditions under which the observations in the two series were made.

The outstanding features are as follows:

The almost constant finding of a lung focus when tuberculous mediastinal glands are present, and the close anatomical relation of those glands to the lung focus.

The frequent singleness of the lung focus.

The constant finding of tuberculous mediastinal glands when a lung focus is present.

The almost constant absence of a lung focus when the portal of entry appears to be elsewhere.

The almost constant absence of evidence that the portal of entry might be elsewhere when a lung focus is present.

These observations, especially when taken in conjunction with the bacteriological findings of Eastwood, F. Griffith, and A. S. Griffith as to the distribution of human and bovine tubercle bacilli, constitute strong evidence in favour of the common existence of primary pulmonary tuberculosis in children.

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2. Eastwood, A., Griffith, F., and Griffith, A. S., *Report to Loc. Gov. Board*, New Series, No. 88, Lond., 1914.

A NOTE ON CERTAIN PHENOMENA ASSOCIATED WITH THE PROTEIN SHOCK REACTION AND INTRAVENOUS VACCINE THERAPY

By A. E. GOW

During the last few months the writer has had occasion to observe in man the reaction following the intravenous injection of various foreign proteins in the form of bacterial emulsions. Attention has been paid in detail to the alterations which take place in the temperature, the pulse-frequency, the blood-pressure, and the differential leucocyte count. Several papers concerning the treatment of arthritis and certain other morbid states by 'protein shock' have appeared since 1916 in various American medical publications.

Protein shock therapy consists in the intravenous injection of a foreign protein and is not necessarily specific. In the reported cases of arthritis the protein employed has been either typhoid or gonococcus vaccine; nearly all the experimental work has been carried out on rabbits with coli-typhoid vaccine.

In the afebrile human subject the intravenous injection of 50–100 million killed typhoid, coli, or gonococcus vaccine is followed by a definite reaction, the so-called 'protein shock reaction'. According to the American authorities a severe chill or rigor ensues in twenty to sixty minutes, lasting for a quarter to half an hour, and accompanied by a rapid rise in temperature; in two or three hours the temperature may have risen five degrees. In several instances a secondary rise, not so high as the primary, has occurred in two to twelve hours. At the height of the reaction nausea and vomiting may be present and severe headache is common. The temperature drops in the course of three to six hours and is normal the following day. The leucocyte count shows an immediate fall, succeeded by a rise to four or five times the normal. In my experience with a coliform vaccine the onset of this rise of temperature has been delayed on occasion for three or four hours, the maximum elevation of perhaps six degrees being reached in six hours, and the fever has not completely subsided for twenty-four hours. This reaction, and that following the intravenous injection of certain other bacterial proteins, will be referred to in more detail later on.

Cecil (1) reports on forty cases of rheumatic fever, acute toxic arthritis, and gonorrhoeal arthritis which were subjected to this form of treatment. In rheumatic fever and 'non-specific' arthritis about 40 per cent. are stated to have

recovered completely in two to ten days, without salicylate, and most of the others were much improved. In rheumatic fever the average number of injections required was two, the dose varying from 30 to 100 million killed typhoid bacilli; salicylate was given if one or two doses of vaccine proved incapable of producing recovery. The seven patients with gonorrhoeal arthritis appeared to benefit but little, if at all, by the vaccine; the injection gave relief for twenty-four hours or more and then the joint pains returned.

Peterson (2) records a case of 'acute multiple arthritis' which received at intervals three doses of typhoid vaccine intravenously, each from 50 to 75 million, and was thereby much improved. The precise nature of the arthritis is not revealed.

Miller and Lusk (3) also report favourable results in the treatment of acute and chronic arthritis by the injection of foreign protein.

Acute disease, other than arthritis, has also been treated, in some cases satisfactorily, by the intravenous injection of typhoid vaccine. In typhoid fever itself both sensitized and unsensitized vaccine have been used by several workers; Gay (4) summarizes their results and adds ninety-eight cases of his own which show a mortality of 6·6 per cent. and thirteen complications. He states that the milder cases of the disease react better to the treatment than the more severe, but even the most severe will in some instances at least be benefited and even aborted. The usual dose of the initial injection was 150 million; the dosage in successive inoculations was slightly increased in order to produce a similar reaction. He states that in typhoid fever the injection is followed in from fifteen minutes to an hour by a chill, which may last for fifteen minutes, and is accompanied by a rise in temperature of one to three degrees, reaching its maximum within three hours and then falling. With the chill is associated a rise in the pulse-rate and there may be slight cyanosis, some respiratory distress, and a sense of discomfort. The temperature reaches normal or subnormal in about twelve hours, with sweating and usually improvement of such symptoms as headache, delirium, &c. If the temperature again rises over a period of two or three days a slightly increased dose is given; if no striking result follows three or four injections at two or three days' interval, very little result from further treatment on the same lines is to be expected. The disease in one-third of the cases in his series was aborted, benefited in another third, while in the remainder it was unaffected; the liability to complications appeared to be diminished, but as a means of preventing relapses the injections are of little value.

According to Gay, these results are due, in part at least, to a non-specific protein reaction which may be produced to some degree by the employment of a number of proteins which have no relation to the typhoid bacillus, e.g. colon bacillus (Kraus), gonococcus vaccine (Ludke), and cholera vaccine; but in the treatment of typhoid fever the typhoid vaccine has the great advantage over other proteins in that it stimulates the production of specific antibody in the patient and so increases his active immunity to the disease. Typhoid vaccine has also been employed intravenously in the treatment of lobar pneumonia

(Scully (5)) and other acute infections. Psoriasis, pemphigus, and certain other chronic diseases of the skin have been treated successfully in similar fashion.

The cases upon which the following observations were made were under treatment at the R.N.A. Hospital for Officers at Peebles, for permission to publish the details of which the writer is indebted to Surgeon Captain W. H. S. Stalkarrt, M.D., F.R.C.S.E., R.N.

Streptococcus Vaccine.

(*a*) A 2nd lieutenant R.M.L.I., aged 29 years, sustained several lacerated wounds of the left leg in the Zeebrugge raid on April 23, 1918. His injuries included a penetrating wound of the muscles of the calf, a wound of the dorsum of the foot, fracturing the second metatarsal bone, and several minor wounds on the outer aspect of the leg. These wounds were cleaned up under an anaesthetic, pieces of metal and wood removed, and a prophylactic dose of antitetanus serum given. About four weeks later he was transferred to R.N.A. Hospital, Peebles, where his wounds appeared to be healing satisfactorily, save for two small ulcers over the lower third of the fibula and a wound measuring about two inches long by one inch broad and three-quarters of an inch deep on the dorsum of the foot. These ulcers were soon covered by a thin greyish slough, their edges became slightly heaped up, and the whole dorsum of the foot considerably oedematous. Various antiseptics and baths were tried; periodically the margins of the ulcer became inflamed, and there was some cellulitis of the foot, with slight constitutional disturbance. The first bacteriological examination of the wound revealed the presence of an anaerobic bacillus and a variety of cocci, none of which appeared to predominate. In the middle of June a small piece of wood was removed from the wall of the ulcer, but as a result there was no indication of healing. Further bacteriological examinations were made, and in the middle of September the predominant aerobic organism was found to be a streptococcus. This was isolated and a vaccine prepared, of which a dose of 40 million was given subcutaneously. A week later the dose was increased, but no obvious change resulted either in the ulcer on the foot or in those above the external malleolus, the floors of which were irregular, apparently not granulating, composed of muscle fibres and other tissue elements covered by a thin grey slough; he suffered considerable pain in the foot, especially at night. A culture five and a half months after the receipt of the injury again showed a streptococcus as the predominant organism; it was isolated pure at the first subculture and an emulsion of 12,000 million in 0·5 per cent. phenol saline put up at 37° C. with 5 c.c. Parke, Davis & Co.'s polyvalent antistreptococcus serum for twelve hours. A sediment formed, but many streptococci remained in the supernatant fluid. This mixture of sediment and serum was diluted with 0·5 per cent. phenol saline to contain 100 million cocci per c.c. for use intravenously.

As the patient had been given a dose of antitetanus serum, and as this brew of vaccine contained a trace of serum, an intradermal test with horse serum, diluted 1 in 10, was performed, to exclude the possibility of anaphylactic shock, before giving the intravenous injection. This test was negative.

On October 12, 1918, he was given intravenously 1 c.c. of the above dilution containing 100 million partly sensitized cocci, made up to 10 c.c. with normal saline; the injection was made very slowly. He dozed off and on that night, but was awake each time his temperature was taken, at two-hourly intervals. Fever was first recorded ten hours later, though his pulse-frequency, which dropped immediately following the injection, had been raised from the fourth hour. Slight headache, which was relieved by aspirin, began at the twelfth hour and persisted for thirty-six hours. Nineteen hours after the injection he

shivered slightly for about ½ hour; his temperature then was 102·4°; an hour later it had risen to 104·2°, when his headache was severe, there was some nausea, he retched once, and on getting out of bed for a moment felt very giddy. During the evening the headache and nausea became less and he slept for 5½ hours on end and was quite comfortable the following morning. The temperature reaction lasted until the eighteenth hour.

The temperature chart of the reaction shows a wave of fever, built of four segments, following an initial fall of eight hours' duration. The first wavelet occupied the tenth to the eighteenth hour, the crest reaching 102·2° at the fourteenth hour; the second and principal one, during which he shivered, extending from the eighteenth to the thirty-eighth hour, shows a maximum temperature of 104·2° at the twentieth hour; the third, from the thirty-eighth to the sixty-second hour, during which 101·8° was the highest recorded and at the end of which the temperature reached normal for the first time, though only to rise again in the fourth wave to 100·8° at the seventy-second hour, finally returning to normal at the eightieth hour.

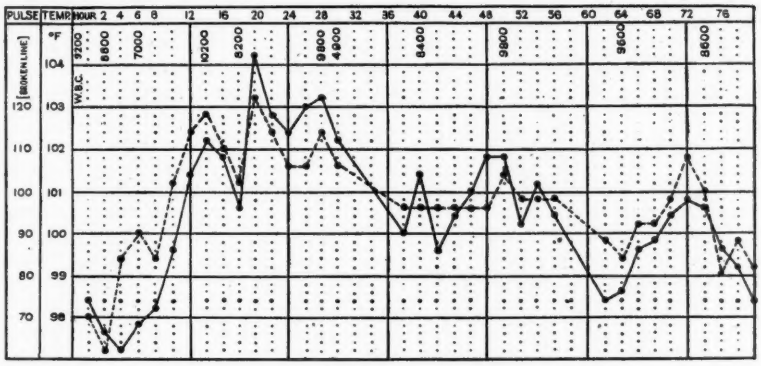

FIG. 1.

The pulse-frequency closely followed the temperature, but, as previously mentioned, it became increased six hours before the onset of the fever and remained slightly raised for some time after the temperature had dropped.

The leucocytes. No leucocytosis was detected, the white blood cells remaining remarkably constant throughout the reaction, nor was any noteworthy change found in the differential count. Unfortunately films were not made at the thirtieth hour, when the only marked deviation was noted. The figures are as follows:

Before injection	9200 per c.mm.
2 hours after	8800 ,,
6 hours	7000 ,,
14 hours	10200 ,,
18 hours (just before rigor)	8200 ,,
28 hours	9800 ,,
30 hours	4900 ,,
40 hours	8400 ,,
50 hours	9800 ,,
64 hours	9600 ,,
74 hours	8600 ,,
144 hours	7000 ,,

The blood-pressure was only recorded twice during the reaction, and it was then about 108/78. His normal is in the neighbourhood of 124/80 mm. Hg.

There was no evidence of splenic enlargement during the reaction.

With regard to the ulcer the result was highly satisfactory. As previously mentioned, the foot was prone to be painful at night; following the injection the nocturnal aching disappeared after the second night. A day and a half after the injection the base of the ulcer appeared much more vascular and there was less discharge; on the sixth day the base was covered with healthy granulations and it was about half as deep as formerly. Steady progress towards complete healing was maintained, and no further injection was necessary.

(*b*) An autogenous streptococcus vaccine was also administered intravenously in a case of long-standing neurofibrositis, but without any apparent benefit to the patient. A Surgeon Commander R.N., aged 48, at the end of the last century had malaria, and in 1905 Malta fever followed by a severe neuritis, after which he was free from pain until 1915. He then had pain, which he describes as 'rheumatic', in the region of the left trapezius and deltoid muscles; this was present for about three months. During the following year he suffered from fleeting pains, seldom lasting more than a day or two at a time, in the tarsus and knees. In September 1917 pain began in the neighbourhood of the left elbow and spread to the scapular region. It persisted, and between January 1918 and the present time he has alternated between hospital and duty. There was no evidence to suggest a latent malarial or M. melitensis infection, and no adequate cause for his pain or focus of infection from which absorption of septic material might take place was found until September 1918, when an extensive pyorrhoea alveolaris was discovered, springing apparently from several old capped teeth. As he was losing weight and his condition growing steadily worse and nothing appeared to check it, his remaining teeth were removed. From the roots of three, after extraction, *Streptococcus salivarius* was isolated in practically pure culture. An emulsion of this organism was put up with Parke, Davis & Co.'s polyvalent antistreptococcus serum; some sediment formed, and the whole mixture was diluted for vaccine purposes. An intradermal test for anaphylaxis to horse serum was negative, and as soon as his gums were healed a dose of 100 million in 10 c.c. of normal saline was given intravenously on October 20, 1918.

The measurable sequelae were comparatively slight. There was no chill, and, though there was some fever from the fourth to the thirty-second hour, the highest temperature recorded was only 100·4° at the twenty-second hour. His pulse-frequency, normally in the fifties, did not rise above 72, and fell to normal with the temperature.

A leucopenia followed the injection, but no leucocytosis was observed up to the fifty-eighth hour, the figures being:

Before injection	5460 per c.mm.
4 hours after	6200 ,,
10 hours after	4600 ,,
22 hours after	2800 ,,
34 hours after	2400 ,,
46 hours after	3800 ,,
58 hours after	4200 ,,

Notwithstanding the seemingly slight constitutional disturbance provoked by the injection and the complete failure to produce a 'shock reaction', his feelings suffered considerably. Within six hours he experienced an exacerbation of pain, and the day following had frequent neuralgic stabbing pains in various situations and a general feeling 'as if he had been well beaten'; headache was sufficiently severe to prevent reading. Not without interest was the development of gastro-intestinal symptoms—dyspepsia, flatulent distension, dry mouth, and furred tongue—suggesting the possibility of a reaction in the alimentary tract consequent on previous absorption of pyorrhoeal discharges. The third day was marked by a general improvement in his symptoms. A second injection was given on the ninth day. As the first was followed by not a little discomfort the

dose of 100 million was not increased; it provoked no rise of temperature and only a slight and transitory acceleration of the pulse. No blood counts were made on this occasion owing to pressure of other work.

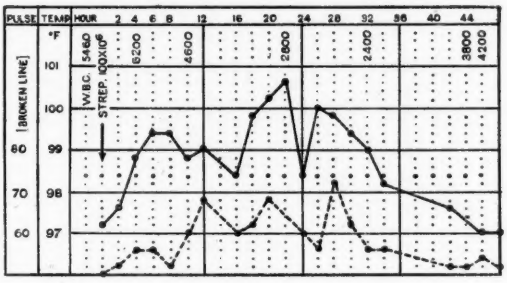

FIG. 2.

Reaction following the Intravenous Injection of a Diphtheroid Organism.

An officer, now aged 33, contracted gonorrhoea in 1909; arthritis supervened, the right knee, left ankle, toe-joints, and back being inflamed for five months. The disease was again acquired in March 1918, the urethral discharge lasting on this occasion for about three weeks. The right knee, left toe-joints, hips, and shoulders became involved almost at once, and he was rendered unable to dress himself, &c. A few doses of a stock gonococcus vaccine appeared to improve him for a time, but he states he made no appreciable progress during the few weeks immediately preceding his admission, in August 1918, to R.N.A. Hospital, Peebles. With the aid of two sticks he walked a short distance with difficulty, and complained of much pain, especially at night, in the knee, heels, shoulders, and hips. There was no evidence of any active arthritis, but muscular wasting around the shoulder and pelvic girdles and of the neck was pronounced. There was no prostatitis, and though a diphtheroid bacillus was the only organism isolated on (his) serum agar after prostatic massage, it was present in considerable quantity.

As so little permanent improvement is reported by American observers to follow an injection of gonococcus or typhoid vaccine in such cases, a vaccine was prepared of this diphtheroid, in lieu of other more pathogenic organism, and a dose of 40 million given subcutaneously. He states he experienced a considerable and undoubted increase of pain, mainly in his shoulders, twelve hours afterwards, and likewise following two succeeding and larger doses. He was of the opinion that his general condition was improved, though progress was very slow. In the hope of speeding his recovery it was decided to give him further doses intravenously.

On October 6, 1918, 200 million in 10 c.c. of normal saline was injected intravenously in 3½ minutes. Save for a little headache and pains in knees, feet, and shoulders, and a slight sensation of chilliness at about the fourteenth hour, there was very little change in his feelings as the result of the injection. His temperature rose two degrees two hours after, and, though it remained raised until the thirty-sixth hour, 99·8° is the highest recorded. The pulse-frequency shows a relatively greater increase than the temperature, though here again the disturbance was slight.

The leucocytes fell somewhat following the injection, returning to the pre-injection figure at the forty-sixth hour.

In spite of there being so little outward and visible sign of any marked reaction to the injection, a week after it the patient declared he felt much stronger and undoubtedly better, and he was anxious for another dose; he abandoned his stick as an aid to walking, even going upstairs, and certainly appeared to rise more easily from the sitting posture and to have less pain.

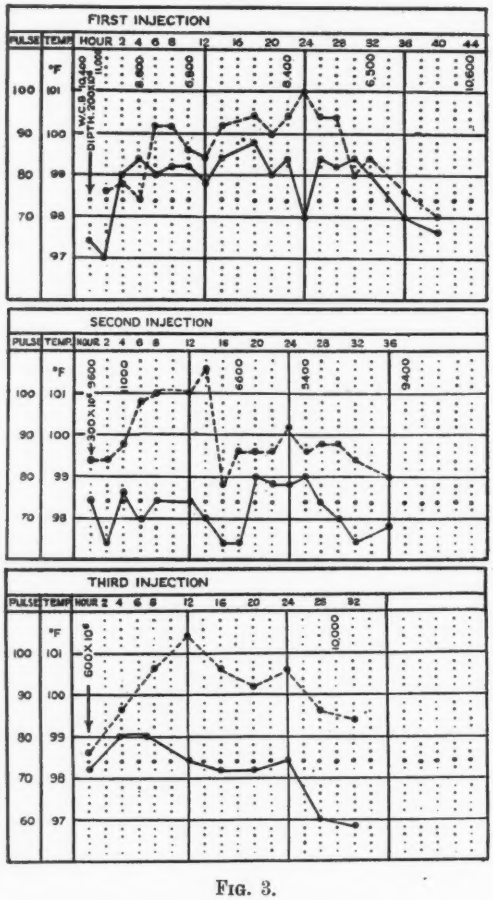

FIG. 3.

Accordingly, eight days after the first intravenous injection, he was given a second one of 300 million; half an hour later he had much pain in feet, heels, and hips. There was even less fever than that following the first injection, the temperature not rising above 99°, and that only between the twentieth and twenty-sixth hours.

The leucocytes again showed a fall.

A third injection, of 600 million, was given a week later; the reaction was feeble, the temperature only reaching 99° from the fourth to the eighth hour, though the pulse showed the same quickening as on former occasions.

The leucocyte counts are as follows:

	1st Injection.	2nd Injection.
16 hours before	10400 per c.mm.	
Just before	11000 ,,	9600 per c.mm.
4 hours after	8600 ,,	11000 ,,
10 hours	6800 ,,	
18 hours		6600 ,,
22 hours	8400 ,,	
26 hours		5400 ,,
32 hours	6500 ,,	
40 hours		9400 ,,
46 hours	10600 ,,	

Influenza.

Two cases of broncho-pneumonia and one of profound toxaemia following influenza were treated with vaccine intravenously. One only, that of a lusty New Zealander, a lieutenant R.N.V.R., aged 25, did not terminate fatally. He contracted the disease in hospital, and as he appeared very ill in the first twelve hours, a swab was taken of his naso-pharynx and plated out on blood agar. A small Gram-negative bacillus, morphologically indistinguishable from Pfeiffer's influenza bacillus, was obtained in practically pure culture. An emulsion of this organism was put up with the serum of a patient recently convalescent from a sharp attack of the disease, but otherwise healthy, and in whose naso-pharynx a like organism had been demonstrated; sensitization of the bacillus appeared to take place.

During the third day this patient's temperature fell from 104·8° to 99·8° and all seemed to be going well, but on the fourth day the temperature shot up again, headache returned, he developed severe pain in the right chest, a frequent painful cough, and brought up a quantity of bright blood-stained sputum, obviously from the lung. Herpetic vesicles rapidly developed on the left lower lip. The same evening movement of the right chest was greatly diminished and percussion much impaired in the axilla and below the right nipple; there was no marked increase of vocal vibrations, but the breath-sounds were very weak in this area, and many fine crepitations were heard, with marked increase of voice sounds.

A film of the sputum showed large numbers of this Gram-negative bacillus, and a few organisms resembling pneumococci. As his leucocyte count was only 6,560 per c.mm., it was considered that the pneumococcus was not the main infecting organism.

His general condition appearing serious, it was decided, with his permission, to give the vaccine intravenously.

A dose of 75 million sensitized bacilli was given intravenously fourteen hours after the onset of the signs and symptoms suggestive of broncho-pneumonia, his temperature at the time being 103·8°. An hour later the temperature was unchanged, but at the second hour it had risen to 105·4°, yet there had been no chill and he volunteered the statement that his headache had gone, his chest was more comfortable, and that he 'felt much better in himself'. Four hours after the injection the temperature had returned to 103·8°; it continued to fall by lysis, being subnormal in seventy-two hours.

The sputum remained blood-stained for twenty-four hours after the injection, when it became more copious and purulent, and the pneumococcus appeared to be the predominant organism. Cough persisted for several days and the signs in the chest slowly cleared.

It is regretted that frequent observations on the behaviour of the leucocytes after the injection were not possible, but no leucocytosis was detected, the highest count recorded being 7,320 per c.mm. at the tenth hour.

The writer does not for one moment bring this forward as a convincing case of the value of intravenous vaccine, but he believes it can at any rate be said that it was productive of no ill effect, and the almost immediate improvement in the general condition of the patient was certainly striking.

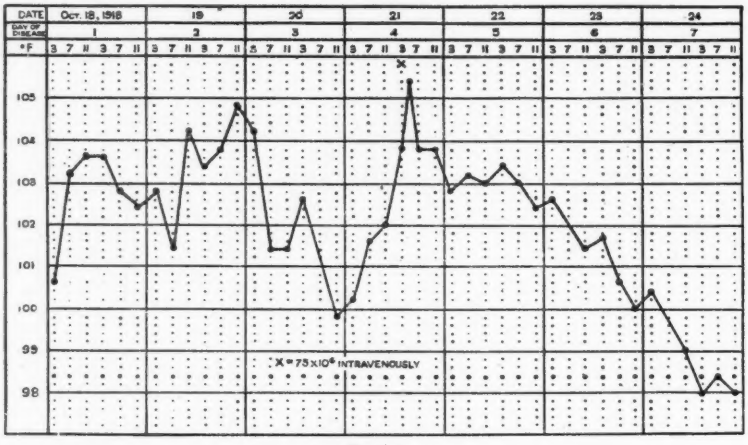

FIG. 4.

One other case of broncho-pneumonia following influenza was given two doses of the same vaccine as a last resort, all usual remedies having failed. The patient had reached the seventh day of pneumonia and was going rapidly downhill. On this day the temperature, which had been constantly between 104·4° and 105° for four days, fell to 103·4°, but showed an upward tendency with a rapidly rising pulse-rate towards evening, and she was vomiting frequently. A Gram-negative coccus, but no influenza-like bacilli, were seen in the sputum.

A dose of 50 million in 500 c.c. of normal saline was given intravenously. The temperature rose to 106° for less than half an hour two hours later, but there was no rigor. For a few hours her general condition appeared to be distinctly bettered, the vomiting temporarily ceased, and her pulse-rate fell from 136 to 110, all of which may have been due to the saline. During the next day her condition again became worse, and at night she was given a further dose of influenza vaccine, to which was added 50 million of her own Gram-negative coccus in 500 c.c. of normal saline. This caused the temperature to rise one degree for a short time and the vomiting ceased, but she died about fourteen hours later.

A civilian with influenza, in whom the nature of the infection was not determined, and who presented no physical signs of disease in her chest, became profoundly toxaemic, wildly delirious, and exhausted with prolonged high fever. In this case also the influenza vaccine in 500 c.c. of saline was tried as a last resort, but without success. Her movements rendered the injection difficult. A slight rigor was produced, after which the patient was quieter and lucid for a short while, but a relapse occurred, death taking place the following day.

Coliform Vaccine.

(a) Cases having a coliform infection of the urinary tract.

(i) A lieutenant R.N.R., aged 33. Diagnosis: pyelonephritis. This officer, who gave no history of other recent illness, was serving in a yacht on patrol

and escort duties in the North Sea. On August 4, 1918, when at sea, he was seized with sudden precipitate micturition, scalding pain, and strangury. The pain and frequency were less after twenty-four hours, but he was then passing a few clots of blood. On August 7 he felt cold and had lumbar pain, which gradually grew worse until August 9, when he reported 'sick'. Three days later he was admitted to a naval hospital, where coli bacilluria was found and he was given three injections of a stock vaccine.

Six weeks after the onset he was transferred to R.N.A. Hospital, Peebles, feeling weak and easily tired; he looked sallow and toxic. There was slight oedema of both feet and ankles, the heart was not enlarged, and the blood-pressure 130/86 mm. Hg. The right kidney was easily palpable and a little tender; left kidney neither palpable nor tender. Frequency of micturition D. 5, N. 1. Urine pale, 1,012, faintly alkaline with faint trace of albumin. The deposit consisted of pus cells, cells from the urinary tract in large numbers, and a feebly motile coliform bacillus. There were no casts, no red blood cells, no eosinophil cells, no crystals, and no cocci. Tubercle bacilli were not found, and a coliform bacillus was isolated in pure culture; this organism produced acid and gas in glucose and lactose, acid and clot in milk in four days, but did not produce fluorescence in neutral red. His serum failed to agglutinate the freshly isolated bacillus. An emulsion in 0·5 per cent. phenol saline of an eighteen-hour agar culture of the bacillus was put up with his serum, but there was no evidence of sensitization or sedimentation, and the mixture of organism and serum was diluted for vaccine purposes.

On September 23, a few days after his admission, he felt shivery and complained of a dull pain in the back; his temperature that evening was 103·8° and his leucocyte count 16,000, of which 12,480 were polymorphonuclears. No growth was obtained on blood culture. The urine contained 10 per cent. of pus, and the lump in the right renal region was larger and more tender. His temperature fell by lysis, reaching normal on the fourth day, when he was given a subcutaneous dose of 5 million autogenous coliform vaccine, some of which was injected intradermally with a control of normal saline, as a test to exclude the possibility of his being anaphylactic to this organism, though one of the essentials to the development of anaphylaxis, i. e. complete elimination of the antigen, was almost certainly absent in this instance.

By September 29 the leucocytes had dropped to 7,800; there was less tenderness in the flank, though the lump was still easily palpable. He was given a dose of 50 million autogenous vaccine and serum in 10 c.c. of normal saline intravenously; the injection was made very slowly. No ill effects were experienced for 3¼ hours, when he began to shiver though he did not feel cold; these involuntary spasmodic movements lasted for twenty minutes, chiefly affecting the muscles of the legs. As they subsided the pulse became slightly intermittent; he vomited once and complained of slight headache. There was no increase of lumbar pain or tenderness, or in the size of the swelling during the general reaction. The temperature, which reached 103·8° six hours after the injection, was again normal in thirty-six hours, when he was free from abdominal tenderness and the lump was no longer to be felt.

A week later the urine was macroscopically clear, but on centrifuging about twenty pus cells were found per 1/6th″ field. *B. coli* was present in a tenth, but not in a hundredth, c.c. of urine; his serum in dilution of 1 : 10 upwards failed to agglutinate a first subculture in broth of a freshly isolated colony.

On October 8, the tenth day after the first injection, and after a few days' complete absence of symptoms, he complained of a return of increased frequency in the early mornings. The urine appeared slightly turbid and was faintly alkaline to litmus. The small deposit obtained in the centrifuge contained a few pus cells, many swollen and degenerate urinary epithelial cells, and a stray red blood cell or two; there was some tenderness and slight resistance in the right renal region,

but no definite lump to be felt. He had no fever, but the leucocyte count was 14,500.

On this account he was given 75 million in 10 c.c. of normal saline intravenously. Three hours later he began to claudicate and complained of a feeling of tightness in the epigastrium, with slight headache but no nausea. The shaking, which was not so severe as after the first injection, lasted on and off for forty-five minutes. Four hours after the injection his temperature reached 103·8° and was subnormal at the fourteenth hour, but the pulse-rate remained raised for forty hours.

The injection was followed by a complete cessation of all symptoms for a week, when increased frequency of micturition (D. 8, N. 2) again manifested itself. The urine contained *B. coli* in a tenth of a c.c.; a few epithelial cells, but practically no pus, composed the deposit.

Cystoscopic examination by Dr. A. C. Morson showed a localized cystitis confined to the base of the bladder, the orifice of the right ureter being more red than elsewhere; there was no suggestion of stone or of tuberculosis, and no tenderness or swelling to be felt in the right loin. The bladder was washed out daily for a few days with a weak solution of silver nitrate.

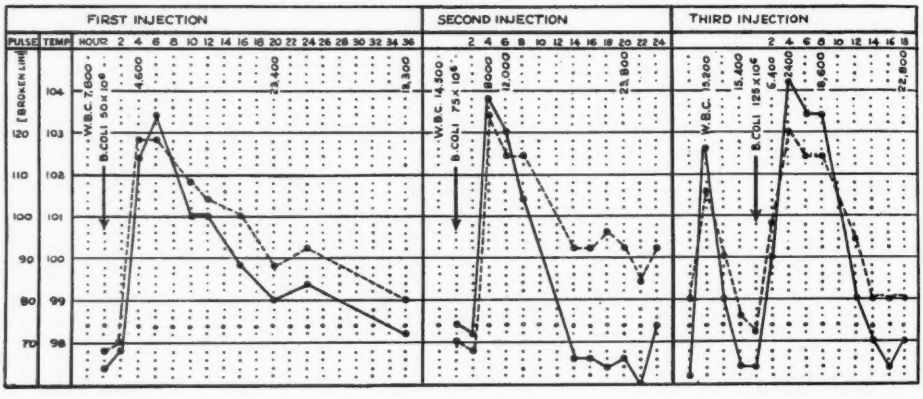

FIG. 5.

On October 17, following a walk in a cold wind, he shivered slightly and had some pain in the back. The temperature was 102·6°, and he had slight abdominal tenderness. The leucocyte count of 15,200 appeared to exclude influenza, which was rampant at the time, for at the outset of that disease no count over 5,000 was registered. The following morning there was a leucocytosis of 15,400, though the temperature was subnormal. An intradermal test with the vaccine was again negative, and he was given 125 million in 10 c.c. of normal saline intravenously. An hour and three-quarters later he was reading, with his arms outside the bedclothes, when he felt 'a wave of coldness' spread over them; it was of short duration. He did not feel generally cold, but 'as though he were going to have a headache'. Shaking of the legs then began and spread slightly to the trunk, lasting for fifteen minutes; half an hour later he experienced a general feeling of coldness and 'slight tremors in the trunk', but no pain or other discomfort.

Eight hours after the injection he was quite comfortable with a temperature of 103·4°, the tenderness in the right renal region having disappeared; the spleen was just palpable on deep inspiration; the enlargement was only transitory. The temperature was subnormal at the fourteenth hour.

In comparing these three reactions of the same patient to increasing doses, viz. 50, 75, and 125 million, of the same vaccine, it is of interest to note that though the severity of the reaction tended to decrease with each succeeding dose, the temperature showed signs of a rise sooner, that it reached practically the same point on each occasion, but fell more quickly, and the muscular twitching accompanying it and general constitutional disturbance were progressively less severe. The pulse at the height of the first two reactions became intermittent, but no irregularity was detected on the third occasion, nor was there ever any cyanosis or respiratory distress; though the pulse-frequency was normal forty-eight hours after the initial injection, it remained raised for some days following the subsequent ones. Vomiting took place in the first instance only. During the chill his systolic blood-pressure fell about 10 mm. Hg and the diastolic about 30 mm. Hg; this observation is not in harmony with the findings of Scully (5), who states there is a rise in blood-pressure after the injection and during the chill, followed by a fall for six hours and return to normal in forty-eight hours. With regard to the leucocytes, this same worker describes a fall at the time of the chill, followed at the end of the first hour by a gradual increase for six hours, with a return to the pre-injection figure at the end of two days. My observations agree with this statement in the main; during the chill the leucocyte count was about half the pre-injection figure, a polymorphonuclear leucocytosis followed, reaching its maximum at about the twentieth hour and then gradually subsiding.

The figures are as follows:

	1st Injection.	2nd Injection.	3rd Injection.
Before	7800	14500	15400
2 hours after			6400 (rigor)
3 hours after		8000 (rigor)	2400
4 hours after	4600 (end of rigor)		
6 hours after		12000	
8 hours after			18600
20 hours after	23400	23800	22800
30 hours after	13300	19400	18600
48 hours after	10200	13800	
68 hours after		8400	

For a month after the third injection the patient remained free from all symptoms and his urine was macroscopically clear, though on centrifuging urinary tract cells and a few leucocytes were always demonstrable. At the end of four weeks he again experienced some discomfort in the loin, the urine became turbid with pus and urinary cells and yielded a copious growth of the coliform bacillus, which was now agglutinated by his serum up to a dilution of 1 : 250 (Dreyer's method). Under an anaesthetic, Dr. Morson filled the right renal pelvis with silver nitrate solution; this was followed by a febrile bout, pain in the back, and a tender enlargement of the kidney. A fortnight later, as the urine still contained many cells and bacilli, it was decided to give a further intravenous dose, for which a fresh brew of vaccine, sensitized with his own serum, was prepared. An intradermal test was again negative. A period of eleven weeks having elapsed since the last injection, the original dose was repeated, 50 million being given intravenously on December 31, 1918.

The reaction was mild; for 3¾ hours he experienced no abnormal sensations, then for forty minutes he felt chilly, with an occasional wave of shivering, slight headache, and nausea. The pulse was occasionally intermittent. As the reaction subsided, he yawned frequently, and had well-marked cutaneous hyperaesthesia. By percussion the spleen was enlarged, but it did not become palpable. The temperature remained subnormal for three hours, at the fifth it reached 102·6°, and was normal at the twenty-first hour.

The systolic blood-pressure (Fig. 6) showed a slight fall immediately after the

injection, followed by a rise of 8 mm. at the end of the chill; by the tenth hour it had fallen 18 mm. below the pre-injection figure, but was normal again at the twenty-fourth hour. The pre-injection diastolic pressure of 62 mm. showed a rise of 20 mm. up to the fourth hour, followed by a fall to 40 mm. at the tenth and twelfth hours and subsequent return to normal. The leucocyte changes are considered in detail below. A week later his urine on two examinations was sterile and free from cells. After six months' freedom from symptoms the same negative result was obtained.

(ii) A lieutenant R.N.R., aged 39, with kyphosis consequent on Pott's disease in childhood, was undergoing treatment in hospital for neurasthenia. A few days after admission, while out walking, he noticed aching in the shins. That night his temperature was 100°; he slept badly, felt shivery, and had pains all over. He continued to suffer from general malaise, though his temperature subsided, and on the third day his urine was heavily blood-stained. A specimen passed first thing in the morning three days later was still dark brown in colour, quite opaque in the flask, and furnished a large deposit of débris. The blood was intimately mixed. The urine was acid in reaction and sp. gr. 1,014. There were far more white cells than could be accounted for by the blood, and numerous swollen cells from the urinary tract were also present, but no casts or crystals were seen. On bacteriological examination a feebly motile atypical coliform bacillus was found in large numbers and pure culture. His leucocytes were 10,900 per c.mm., of which 8,340 were polymorphonuclears. He complained of a dull ache in the right post-renal area, but there was no abdominal tenderness and the kidneys were not palpable; there was no oedema and no clinical evidence of cystitis.

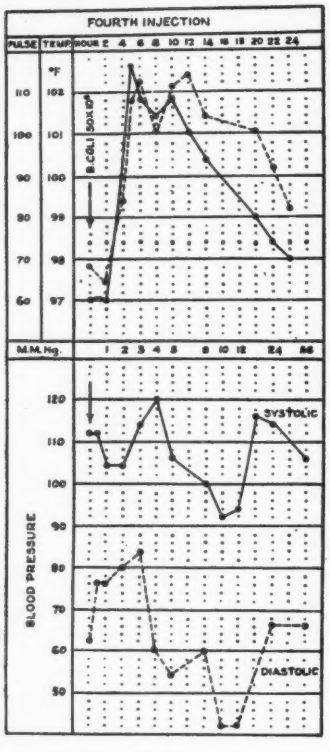

FIG. 6.

Two days later, the urine having become clear, he was examined with the cystoscope by Dr. A. C. Morson. No evidence of growth, cystitis, tuberculosis, or stone was found. The ureteric orifices were not seen, but in the region of the right was a small haematoma. There was no stricture and the prostate and testicles were normal. As the dull ache in the right post-renal area persisted, it was inferred that the right kidney pelvis was infected. The following day he had a febrile bout similar to that referred to above and associated with pain in the limbs and back of the neck. There was no return of haematuria, though the urine contained 4 per cent. of pus by volume.

The reaction following the intravenous injection of 75 million autogenous coli was, as regards constitutional disturbance, comparatively mild. He had no subjective sensations for three-quarters of an hour, but then, without feeling cold, he began to shiver. This continued for twenty minutes, and he began to feel chilly; headache and sacralgia developed. Meanwhile the temperature was rising, and the leucocyte count and blood-pressure showed a marked fall. During the fourth hour his complaint was of nausea, headache,

pain in the back of the neck, hips, and shoulders, and aching in the shins—all very similar to that experienced in the two previous febrile attacks; he vomited once, after which he rapidly improved, and at the seventh hour was up for a short time. The day following he felt in his usual health. The highest temperature recorded was 101·6°, when the leucopenia was over, at the sixth and seventh hours; an hour later it had dropped to 100·2°; a secondary rise of 1° was noted at the ninth hour; thereafter a fall by lysis occurred, normal being reached at the seventeenth hour. The pulse-frequency throughout the reaction showed a relatively greater disturbance than the temperature; at the fourth and fifth hours it was 132, and it became slightly irregular for a short period as the rate decreased. There was no clinical evidence of any local reaction in the urinary tract as the result of the injection; by percussion the spleen was appreciably enlarged, but it did not become palpable.

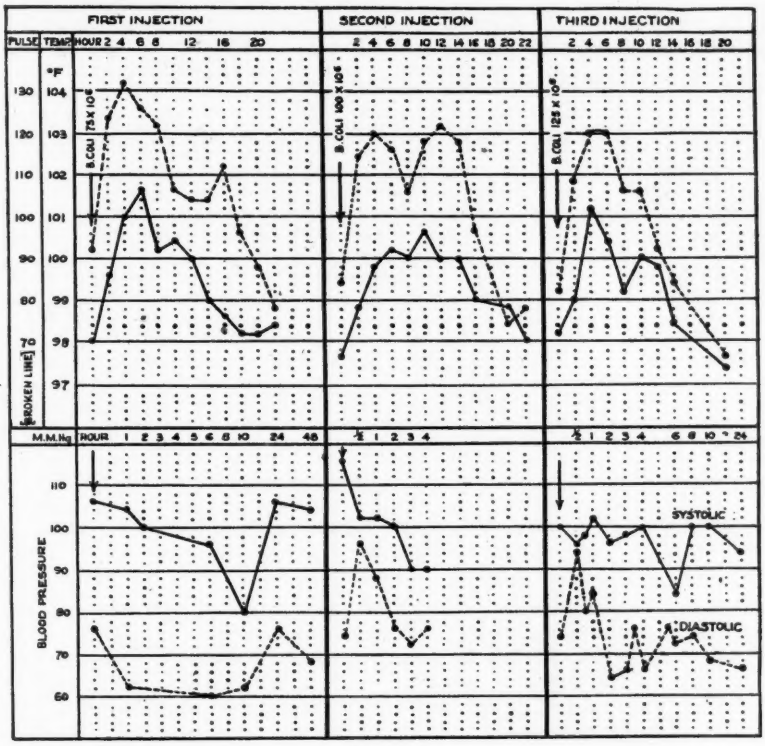

FIG. 7.

The blood-pressure showed a marked fall. Before the injection it was 108/76; after the rigor 100/64; at the seventh hour 96/60; at the twelfth hour 80/62. It remained constant at the pre-injection figure after twenty-four hours.

A second injection was given ten days later, the dose being increased to 100 million. The reaction symptoms were similar in kind but less in degree, though as the reaction subsided restlessness, yawning, and cutaneous hyperaesthesia were prominent; he felt quite well at the seventh hour. The third injection, of 125 million, given after an interval of six days, produced but a slight sense of discomfort, though the temperature reaction was only a little less severe.

Half an hour after the second and third injections the systolic and diastolic

blood-pressures were found to closely approximate—on the first occasion the readings were 102/96, and on the second 96/94, giving a pulse-pressure of 6 and 2 mm. respectively. This state of affairs was of very short duration, for before the end of the hour the diastolic pressure had fallen to 88 and 84. The lowering of both systolic and diastolic pressures was more noticeable after the second than the third injection.

(*b*) *Case in which Coli Vaccine was used to produce a 'Shock Reaction'.*

The following is an example of a reaction of unusual severity.

The patient is he whose previous history is recorded in Case 2 of the streptococcus series. As the pains in his extremities were not improved by the streptococcus vaccine, and no 'shock reaction' had been produced by those injections, and as he had derived no appreciable benefit from a full course of 'phylacogen' subsequently undertaken, it was decided to produce a 'shock reaction' with coli vaccine, in the hope of bettering his condition.

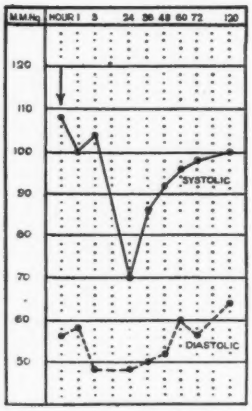

FIG. 8.

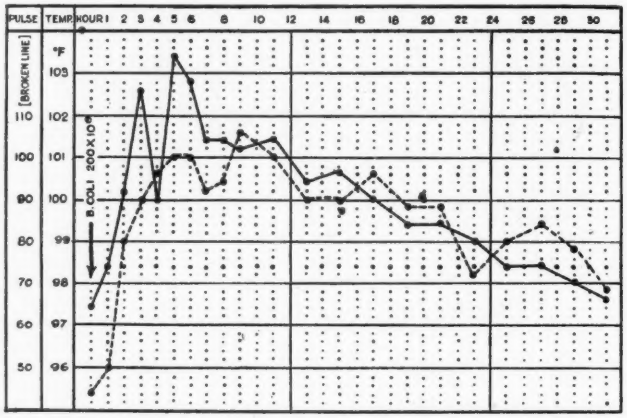

FIG. 9.

He was given intravenously a dose of 200 million coli in 10 c.c. of normal saline. He was as usual until the end of the first hour, and then developed somewhat suddenly 'a feeling as though he had a bad attack of influenza'—headache and general pains in the limbs, especially the shins. At this time his temperature, though rising, was not above normal, and his leucocytes had fallen to 1,200 per c.mm. Shortly after he felt cold and restless and was constantly altering his position in bed; there was no cyanosis or respiratory distress. During the second hour fever developed and a few small waves of involuntary spasmodic muscular contractions passed over him, but there was no general rigor; he felt ill with pains in the large joints and severe eyeball and temporal ache, yet no nausea. At the third hour headache was somewhat better (no rise yet in the white blood cells), but pain was severe in the legs. During the fourth hour he vomited eight times, sweated a little, felt faint and complained of pain in the head, sacral region, and limbs, but from then onwards he slowly improved. The highest temperature recorded was 103·4° at the fifth hour; it reached normal at the twenty-fifth hour. The curve of the pulse-frequency follows closely that of the temperature; no irregularity in cardiac rhythm was noted. Coincident with the lessening of the fever was the rapid increase of the leucocytes in the peripheral

blood, their number reaching 32,000 per c.mm. at the twenty-fourth hour. (The blood-changes are considered in greater detail below.) Throughout the reaction the blood-pressure showed a steady fall, dropping from 108/56 to 70/48 at the twenty-fourth hour; the pre-injection reading was not regained until the fifth day. There was no clinical evidence of splenic enlargement.

Convalescence was impeded by an extensive herpetic eruption involving the margin of nose and mouth, mucosa of lips, tongue, palate, and anus, which appeared on the fourth day, though considerable soreness of the affected areas was complained of previously; there were also localized painful areas on the scalp and loss of appetite. It was ten days before the constitutional disturbance was fully past. According to Auld (11), facial herpes may also occur after the intravenous injection of colloidal platinum.

His pains were certainly lessened, at any rate for a time, after the injection, and his general condition improved.

Cytological Changes in the Blood following the Injection of B. coli Vaccine.

The alteration in the cellular constituents of the blood shows a striking similarity in the above cases.

The intravenous injection caused an almost immediate fall in the white blood cells, in which polymorphonuclears, lymphocytes, and large mononuclears are all early involved, though eosinophil and basophil cells stand fast until later.

Following a first injection, the retreat of the polymorphonuclears from the peripheral circulation is extremely hurried, and in each of two instances they were outnumbered by the lymphocytes at the end of the first hour, being only 577 and 288 per c.mm. respectively. By the second hour they had rallied somewhat, and at the fourth reached the pre-injection figure, after which a more rapid increase took place, the maximum being recorded at the twenty-fourth hour, 19,224 and 29,624 per c.mm. respectively; this rise is succeeded by a fall during the next forty-eight hours to the pre-injection figure, the whole cycle occupying approximately seventy-two hours.

The 'Arneth count' as modified by Cooke (6) shows an early, and later very marked, dislocation to the left, i.e. the neutrophil leucocytes with undivided nuclei, or not more than one chromatin filament in the nucleus, vastly outnumber those with three or more divisions, and not until the subsidence of the leucocytosis were any cells of Classes IV and V encountered. During the leucocytosis several neutrophil myelocytes were found in all cases. Normoblasts also occurred in small numbers in the blood of one case at the seventh and twenty-fourth hours, and a few erythrocytes showed well-marked basophilic stippling. (Though this patient was complaining of much pain in the legs, I was unable to satisfy myself that there was any definite tenderness of the bones.)

Though the fall in the lymphocytes is less abrupt, it is a very striking feature and of far longer duration than the polynuclear leucopenia. For the first half-hour little change is manifest, but before the hour is passed the departure of many lymphocytes from the peripheral blood is apparent, and the exodus continues for two or three hours; 162 and 168 per c.mm. are the lowest figures, recorded at the third and fifth hour in the respective cases. By the eleventh hour there is some indication of recovery, after which a gradual rise restores to

normal this feature of the blood-picture at about the forty-eighth hour. There is no lymphocytosis. After second and third injections the polynuclear leucopenia is found to be of shorter duration, and the leucocytosis more rapid in development, though less sustained. The lymphocytes, however, do not disappear so early from the peripheral circulation, and even with later injections show signs of an actual increase before the fall sets in.

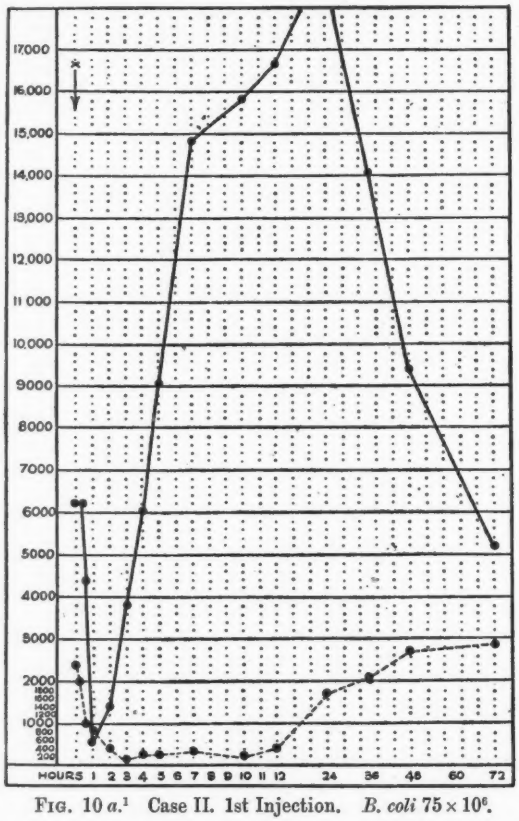

FIG. 10 *a*.[1] Case II. 1st Injection. *B. coli* 75×10^6.

The mechanism whereby improvement in the clinical condition of the patient is brought about in certain cases as a result of the protein shock reaction is largely a matter of conjecture, and several are the guesses that have been made to explain it. When the specific infecting organism is employed as the protein a favourable result is easier to understand. That the production of a high leucocytosis is not an essential to marked improvement in the lesion for which the treatment is undertaken is evident, for in the first of the streptococcus cases above referred to, and the only one in which a 'shock reaction' was provoked, the highest count observed was only 10,200 per c.mm., and that on one occasion only.

[1] In this, and in subsequent diagrams, the continuous line indicates polymorphs, the broken line lymphocytes.

It is perhaps worthy of note that no leucocytosis was observed after the intravenous injection of streptococcus, diphtheroid bacillus, or 'influenza' bacillus; the coliform being the only type that evoked a striking leucocytic response. Cecil mentions a leucocytosis following gonococcus injection. Andrewes (7), in the Croonian Lectures of 1910, demonstrates as an immunity reaction the initial, or anaphylactic, leucopenia followed by leucocytosis consequent on the intravenous injection of various bacteria. He found the coli-typhoid group the most highly developed of bacteria in inducing this initial leucopenia in rabbits, that

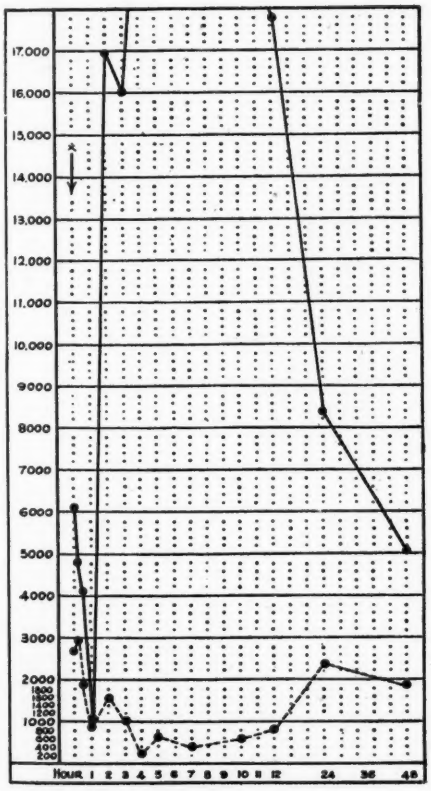

FIG. 10 *b*. Case II. 2nd Injection. *B. coli* 100×10^6.

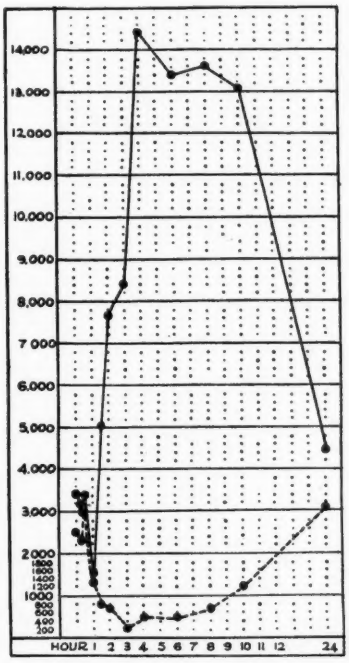

FIG. 10 *c*. Case II. 3rd Injection. *B. coli* 125×10^6.

staphylococci and diphtheroids have the power only feebly developed, and in ordinary circumstances the injection of streptococci was productive of leucocytosis without leucopenia. Though the dosage for the rabbit was relatively far greater than that employed in human cases, the similarity of the resulting leucocytic response to coli injection in the two species is very striking; with the other bacteria under consideration the initial leucopenia was the only feature observed in man. It has yet to be fully explained why the typhoid bacillus, dead or alive, excites a leucocytosis when injected intravenously into man, whether sick of typhoid fever

or not, whilst leucopenia, except perhaps at the very onset, is the characteristic state of typhoid septicaemia naturally acquired; in the former case the leucocytosis is probably due to the bacillus playing the part of a protein and not that of the specific infecting agent as in the latter. It is of interest to note in this same connexion that the influenza bacillus, also associated in diseased man with relative leucopenia, failed to induce leucocytosis when injected intravenously in a case referred to above; this cannot have been due to marrow exhaustion, for the patient recovered.

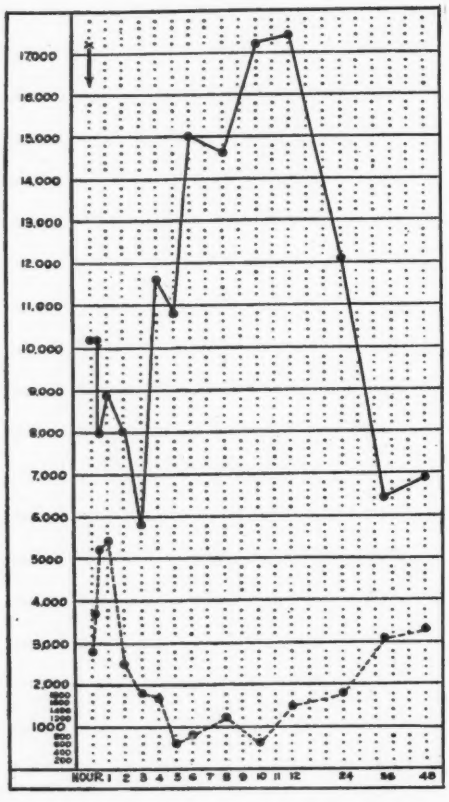

FIG. 11. Case I. 4th Injection. *B. coli* 50×10^6.

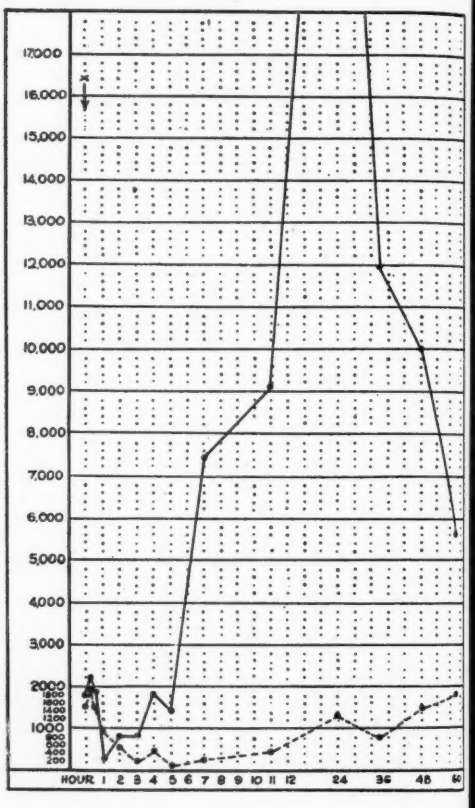

FIG. 12. Case III. 1st Injection. *B. coli* 200×10^6.

Andrewes found this reactive polynuclear leucocytosis better marked in the immune than the normal animal, but McWilliams (8) states that a typhoid immune and a normal rabbit respond with an equal degree of leucocytosis to an intravenous injection of typhoid bacilli, and a typhoid immune rabbit shows the same grade of hyperleucocytosis when injected with *B. coli* as with *B. typhosus*. In my human cases to which three or more injections were given the reactive leucocytosis was approximately equal in each instance, but the initial, or anaphylactic, leucopenia developed more rapidly and was of shorter duration

with each succeeding dose, showing that there is a distinct relationship between the degree of immunity and the intensity and abruptness of the polynuclear leucopenia; with increasing immunity the stage of lymphocytic leucopenia is also more prolonged. There is some evidence to suggest that a sensitized vaccine is a more potent agent for the production of hyperleucocytosis in normal animals than is a simple bacterial emulsion (Gay and Claypole). Andrewes proved that during the initial peripheral leucopenia the polymorphonuclear leucocytes are congregated in the pulmonary capillaries; during the reactive leucocytosis which follows the intravenous injection of coli vaccine in man, the Arneth nuclear count and the presence of neutrophil myelocytes and normoblasts in the peripheral blood point to overaction on the part of the bone-marrow, and thus the increase is to be accounted for in the main by the throwing out of new cells from the factory, rather than by a return of those leucocytes which were incarcerated in the lungs.

In the septicaemic stage of typhoid fever the rapid disappearance of living organisms from the blood-stream following the intravenous injection of vaccine has been demonstrated.

The protein shock reaction is also accompanied by definite chemical and physical changes in the blood serum. Petersen (2) describes certain ferment-antiferment changes and considers binding of the antiferment plays an important part by setting the ferment free to act; ereptase he considers a detoxicating agent aiding in the elimination of toxic products, while cases that do not show any clinical improvement as a result of the injection seldom show an increase in peptidase.

Culver (9) finds an increase in the specific bacteriolysin and opsonin following injections of gonococcus vaccine, or of proteose, such increase being more marked after the first injection, and indeed with subsequent ones a decrease may occur despite continued improvement in the clinical condition of the patient. In typhoid fever treated by intravenous injection of vaccine Inez Smith has demonstrated a greater rise in the opsonic index in those that were 'abortively cured' than in either the 'benefited' or 'unaffected' cases—and this in spite of the fact that it is apparently not the polymorphonuclears that play the main part in our defence against the *Bacillus typhosus*. The agglutination titre also is increased. Teague and McWilliams (10) showed that in rabbits the intravenous injection of a suitable dose of killed typhoid bacilli causes within twenty-four hours a 'refractory state' which enables them to withstand a dose of living typhoid bacilli that is fatal to normal rabbits; specific antibodies are not demonstrable in the serum until four or five days after the injection of antigen. They further found that the bacteriolytic power for typhoid bacilli of normal and highly immune antityphoid serum is unaltered by the intravenous injection of a large dose of typhoid bacilli, yet the serum of a rabbit that has received only one or two immunizing injections shows a distinct, but not a marked, rise in bacteriolytic titre five and twenty-four hours after such an injection. They have suggested that the therapeutic effect of such an injection in man may be due to the increased passage of antibody-containing serum into the lymph channels.

Table of Differential Leucocyte Counts after Intravenous Injection of B. coli Vaccine

Time.	Case II. 1st Injection.		Case II. 2nd Injection.		Case II. 3rd Injection.		Case III. 1st Injection.		Case I. 4th Injection.	
	%	per c.mm.	%	per c.mm.	%	per c.mm.	%	per c.mm.	%	per c.mm.
Before										
Total		9000		9680		6800		3680		13600
Polym.	69·0	6210	64·0	6195	50·5	3434	48·5	1785	75·0	10200
Lympho.	26·5	2385	28·5	2760	37·0	2516	42·0	1545	21·0	2856
Large mono.	3·0	270	3·5	339	4·5	306	6·5	240	2·5	340
Eosino.	1·5	135	2·5	242	5·5	374	2·0	73	0·5	68
Baso.	—	—	1·5	134	2·5	170	1·0	37	1·0	136
5 minutes after										
Total		8960		8280		6400		4440		14900
Polym.	70·5	6318	58·5	4840	51·0	3264	50·0	2220	69·0	10281
Lympho.	23·0	2060	36·0	2980	37·0	2368	43·5	1931	25·0	3725
Large mono.	5·0	448	3·5	290	6·0	384	4·0	178	3·5	522
Eosino.	0·5	44	1·5	120	5·0	320	1·0	44	1·5	233
Baso.	1·0	90	0·5	40	1·0	64	1·5	67	1·0	149
½ hour										
Total		5720		7000		7500		3760		14000
Polym.	77·5	4433	59·5	4165	46·5	3488	50·5	1899	57·0	7980
Lympho.	17·5	1001	27·5	1925	41·0	3075	41·0	1541	37·5	5250
Large mono.	1·0	57	8·0	560	3·5	263	3·5	132	3·0	420
Eosino.	3·0	172	3·0	210	7·5	562	2·5	94	0·5	70
Baso.	1·0	57	2·0	140	1·5	112	2·5	94	2·0	280
1 hour										
Total		1480		2440		3280		1200		15300
Polym.	39·0	577	48·0	1170	48·0	1574	24·0	288	59·0	8927
Lympho.	55·0	814	38·0	924	41·5	1363	71·0	852	34·75	5416
Large mono.	3·5	51	4·5	110	1·5	49	2·0	24	3·75	574
Eosino.	2·0	30	8·0	200	6·0	196	1·5	18	2·0	306
Baso.	0·5	8	1·5	36	3·0	98	1·5	18	0·5	77
1½ hours										
Total						6400				
Polym.					81·0	5184				
Lympho.					13·0	832				
Large mono.					2·0	128				
Eosino.					1·0	64				
Baso.					3·0	192				
2 hours										
Total		1920		19000		8760		1480		11500
Polym.	74·5	1430	89·25	16960	89·0	7796	53·5	792	70·0	8050
Lympho.	22·0	422	8·75	1660	8·5	744	40·0	592	22·0	2530
Large mono.	1·5	29	0·5	95	1·0	88	3·5	52	3·0	345
Eosino.	1·5	29	1·5	285	1·0	88	2.0	29	2·0	230
Baso.	0·5	10	—	—	0·5	44	1·0	15	3·0	345
3 hours										
Total		4040		17400		8840		1080		7900
Polym.	95·5	3858	93·0	16183	95·0	8442	73·0	788	74·0	5846
Lympho.	4·0	162	5·75	1000	3·0	266	22·0	238	24·0	1896
Large mono.	0·5	30	1·0	174	0·75	66	3·0	34	1·5	118
Eosino.	—		0·25	43	0·5	44	1·0	10	0·5	40
Baso.	—		—	—	0·25	22	1·0	10	—	—

Table of Differential Leucocyte Counts (continued).

Time.	Case II. 1st Injection.		Case II. 2nd Injection.		Case II. 3rd Injection.		Case III. 1st Injection.		Case I. 4th Injection.	
	%	per c.mm.	%	per c.mm.	%	per c.mm.	%	per c.mm.	%	per c.mm.
4 hours after										
Total		6360		21600		15400		2400		13600
Polym.	94·5	6010	97·25	21006	93·0	14322	76·0	1824	85·75	11662
Lympho.	4·5	286	1·25	270	3·5	539	21·0	504	12·75	1734
Large mono.	0·5	32	0·25	54	1·0	154	2·0	48	1·0	136
Eosino.	—	—	0·75	162	1·5	231	1·0	24	0·25	34
Baso.	0·5	32	0·5	108	1·0	154	—	—	0·25	34
5 hours										
Total		9760		25000				1680		11600
Polym.	93·5	9125	95·25	23812			85·5	1438	93·0	10788
Lympho.	3·0	293	2·75	688			10·0	168	5·25	509
Large mono.	1·0	97	1·25	312			2·5	42	1·0	116
Eosino.	2·0	195	0·25	63			0·5	8	0·25	29
Baso.	0·5	50	0·5	125			1·5	24	0·5	58
6 hours										
Total						14500				16400
Polym.					92·5	13412			92·25	15129
Lympho.					4·0	580			5·0	820
Large mono.					1·0	145			2·25	369
Eosino.					2·5	363			0·5	82
Baso.					—	—			—	—
7 hours										
Total		15600		26400				7760		
Polym.	95·0	14820	96·75	25542			95·0	7372		
Lympho.	2·0	312	1·75	462			3·0	233		
Large mono	2·5	390	1·0	264			0·5	39		
Eosino.	0·5	78	0·25	66			1·0	77		
Baso.	—	—	0·25	66			0·5	39		
	Myelocytes						Normoblasts			
8 hours										
Total						14800				16200
Polym.					92·25	13653			90·0	14580
Lympho.					5·0	740			8·0	1296
Large mono.					1·0	148			2·0	324
Eosino.					0·25	37			—	—
Baso.					1·5	222			—	—
10 hours										
Total		16400		21600		15300				18400
Polym.	96·5	15826	94·75	20466	86·75	13186			93·75	17250
Lympho.	1·25	205	3·0	648	8·25	1254			3·75	690
Large mono.	1·75	287	0·75	162	2·0	304			1·75	322
Eosino.	0·5	82	1·0	216	1·75	266			0·25	46
Baso.	—	—	0·5	108	1·25	190			0·5	92
	Myelocytes								Myelocytes	
12 hours										
Total		17500		19000				9800		19200
Polym.	95·25	16668	93·5	17765			3·5	9163	90·25	17328
Lympho.	2·75	482	4·5	855			5·0	490	8·0	1536
Large mono.	1·75	306	1·25	238			1·0	98	1·25	240
Eosino.	0·25	44	0·5	95			—	—	0·25	48
Baso.	—	—	0·25	47			0·5	49	0·25	48
									Myelocytes	

Table of Differential Leucocyte Counts (continued).

Time.	Case II. 1st Injection.		Case II. 2nd Injection.		Case II. 3rd Injection.		Case III. 1st Injection.		Case I. 4th Injection.	
	%	per c.mm.	%	per c.mm.	%	per c.mm.	%	per c.mm.	%	per c.mm.
24 hours after										
Total		21600		11600		8800		32200		14600
Polym.	89·0	19224	72·5	8410	51·0	4488	92·0	29624	83·5	12191
Lympho.	8·0	1728	21·0	2436	35·5	3124	4·0	1288	13·0	1898
Large mono.	2·5	540	3·5	406	6·5	572	2·75	885	1·5	219
Eosino.	0·25	54	2·0	232	5·0	440	0·5	161	1·5	219
Baso.	0·25	54	1·0	116	2·0	176	0·75	242	0·5	73
							Normoblasts & myelocytes		Myelocytes	
36 hours										
Total		17000						13400		10300
Polym.	83·5	14195					89·0	11926	63·0	6489
Lympho.	12·5	2125					6·0	804	30·5	3142
Large mono.	3·0	510					4·5	603	4·0	412
Eosino.	0·5	85					0·5	67	1·0	103
Baso.	0·5	85					—	—	1·5	154
							Myelocytes			
48 hours										
Total		13000		8000				12400		10800
Polym.	72·5	9425	64·5	5160			81·0	10004	64·0	6912
Lympho.	21·0	2730	24·5	1960			12·0	1488	31·0	3348
Large mono.	4·5	585	3·5	280			4·5	558	4·0	432
Eosino.	2·0	260	6·0	480			1·5	186	1·0	108
Baso.	—	—	1·5	120			1·0	124	—	—
60 hours	(72 hours)									
Total		10000						8000		
Polym.	62·5	6250					70·0	5600		
Lympho.	29·5	2950					23·0	1840		
Large mono.	4·5	450					5·5	440		
Eosino.	3·0	300					1·0	80		
Baso.	0·5	50					0·5	40		

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ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

THE TWELFTH ANNUAL GENERAL MEETING was held in London on Friday and Saturday, July 11 and 12, 1919, at No. 1, Wimpole Street, by kind permission of the Royal Society of Medicine.

The minutes of the previous meeting were read and confirmed, the Officers and Executive Committee for the year and new members elected, the Accounts presented, and the invitation of Manchester for next year's meeting accepted.

The scientific business of the meeting followed.

Prof. J. B. Leathes (introduced) gave the results of a study of the function of the nephritic kidney.

1. Diuresis takes place after ingestion of water as in the normal.

2. Normal response to the ingestion of water includes a rise in alkalinity. This occurs, in varying degree, in the nephritic.

3. Normal urine is highly acid at night, but hyperpnoea raises alkalinity at once, and the diurnal alkaline tide, which is not dependent on food, is probably connected with respiration. In nephritis urine is more acid than normal, therefore the kidney does not hold back acid, but apparently more is formed.

Discussed by Drs. Poulton and Lister, and Mr. Mackenzie Wallis.

Sir Clifford Allbutt related two cases of chronic parenchymatous nephritis, with extreme dropsy, which latter feature rapidly disappeared under Epstein's diet, after all ordinary means, including salt starvation, had failed. In the former case, a young male, the albumen also disappeared almost completely while the patient was on ordinary diet at his own house.

Discussed and corroborated by Drs. Caton, Poulton, Francis Boyd, Parkes Weber, and the President.

Sir Archibald Garrod stated that cystinuria was evidence of an abnormal protein metabolism. Cystin was a decomposition, not a synthetic product. Cystinuria was a family complaint, though often undiscovered until the urine was searched for crystals. He believed that cystin calculi would be found to arise like other calculi, though no organic nucleus had yet been found.

Discussed by Mr. Mackenzie Wallis.

Dr. George Graham said that diabetes innocens was found—

1. In persons with diseased kidneys.

2. In a more numerous class whose kidneys and blood were normal.

3. In a small group who, though hypoglycaemic, pass more sugar than the second class, even up to 4 per cent., and are never sugar-free, though ingested sugar does not affect them like true diabetics. These respond differently from the other groups, and are liable to be mistaken for mild diabetics.

Discussed by Drs. Parkes Weber, who complained that the term diabetes was in this instance misapplied, since polyuria was absent, Langdon Brown, who warned the audience that hypoglycaemia was not sure evidence of future innocence, and Hobhouse.

Mr. Mackenzie Wallis (introduced) said that an excess of diastase in the urine, together with a positive Loewe reaction and glycosuria, was evidence of disease of the

pancreas, but that it might vary in amount, and tended to decrease during the progress of the disease.

Discussed by Dr. Langdon Brown, who ascribed the symptom to obstruction rather than insufficient action of the pancreas, adding that it distinguished this form of glycosuria from diabetes, and was also of value in the prognosis of nephritis, and by Sir A. Garrod, who insisted on the importance of the tripod of symptoms, any one of which singly was relatively insignificant.

Dr. E. I. Spriggs, from a large series of gastric analyses, concluded that—

1. 70 per cent. of hyperacid cases are due to causes other than gastric or duodenal ulcer or appendicitis.

2. The relief of pain by food is as common in hypo- as in hyper-acidity.

3. Irritability of the duodenal cap (shown by X-rays) is not peculiar to hyperacidity.

Discussed by Dr. H. L. Tidy, who asked if hyperacidity is ever due to organic acid.

Dr. E. P. Poulton and Dr. T. R. Parsons (introduced) gave values for the hydrogen ion concentration of the blood in pathological states measured at the corresponding alveolar CO_2 pressures. In uraemic coma the value was increased, and the same was true of a case of diabetes. In cases of primary cardiac failure, and in a case of diabetes, the value was diminished. The buffer value of the blood as measured by the alteration of pH, due to a difference of 5 c.c. CO_2 in 100 c.c. of blood, was normal.

Sir W. Osler showed pictures of multiple hereditary naevi, spoke of the severe anaemia caused by them, usually by way of epistaxis, and remarked that some of them take the form of tumours on the lips or tongue. They were usually congenital.

Discussed by Drs. Parkes Weber and George Murray.

Dr. Francis Boyd described pellagra seen in Turkish prisoners and Armenian refugees. The chief symptoms were—

1. Pigmentation of the hands, then of the face, then of any part of the body under pressure. Dryness, even under pilocarpin, of the pigmented areas.

2. Wasting, mental depression, natural temperature.

3. Tongue bare and moist, angle of mouth fissured, achlorhydria, inefficient intestinal digestion, indicanuria, offensive stools.

4. Low blood-pressure, natural C.S. fluid.

It is due to lack of protein, and is cured by liberal diet. No parasite was found in the blood.

Discussed by Dr. Cecil Wall.

Dr. A. R. Parsons and Dr. John Speares (introduced), from two cases of chronic splenomegalic haemolytic icterus, a father and son, concluded—

1. That this disease is not incompatible with good working health for many years.

2. That syphilis, notwithstanding Hayem's opinion, is not the cause or in any way necessary for its production; Wassermann was in their case, as in Weber's cases, quite negative.

3. That X-rays produce no diminution in the size of the spleen.

4. That the blood may be kept at almost a normal count by good feeding and occasional periods of rest.

5. That while clinically there may be no detectable lesion and no evidence of any disease on microscopical examination, there is in the aldehyde reaction some reason for believing that the liver is not normal, and it is now proven that the icterus is not of hepatic origin.

6. That while there is therefore reason for believing that the bilirubin is not formed in the blood-stream directly by haemolysis of the R.B.C., it is certain that the bile is not the cause of the haemolysis.

7. That bile in the blood-stream, instead of increasing the fragility of the R.B.C., has rather a tendency to increase the resistance of the R.B.C. to haemolysis.

8. That icterus is not a necessary sign of this condition, and consequently the present name of haemolytic icterus is not quite accurate. Too much importance has been assigned to the jaundice, and in the light of present knowledge the two outstanding signs are splenomegaly and increased fragility of the R.B.C.

Discussed by Dr. Parkes Weber and Sir William Osler, who were adverse to operation, and by Sir B. Dawson, who favoured it. Drs. Charles and Turney gave evidence of its connexion with gall-stones.

Dr. Gilman Moorhead contrasted two cases of infantilism of which one gave no evidence in life of pancreatic disease, and dying of influenza showed a normal pancreas and pituitary, but an involuted thymus. The reproductive organs were undeveloped, the skeletal ossification delayed, and the intestines swarming with *Trichocephalus dispar* and Gram + bacteria. The second had typical creamy stools from which fat separated, and in which muscle fibres were plentiful. She was greatly improved by pancreatic extract, and began to develop the breasts.

Dr. P. Hamill related two cases of kala-azar from Mesopotamia, treated by rising doses of antimony with good results. No parasite was found.

Discussed by Sir A. Garrod, who had seen and successfully treated with antimony four cases, of which three at least were infected in Malta.

Colonel John Nixon stated that in wounds of the chest early operation was indicated by—

1. Shock.
2. Severe pain.
3. Dyspnoea.
4. The character of the wound.

Contralateral collapse is rare and is a hindrance to operation. Surgical emphysema conceals all signs but the apex beat, and implies pneumothorax. Large foreign bodies should be removed. Abnormal heart-sounds occur without gross injury to the heart. Diaphragmatic injury must usually be repaired. It, and also spinal injury, are sometimes difficult to diagnose. X-rays are necessary for the diagnosis of retained foreign body, and of the condition of the missile's track, and are the best means for diagnosing haemo- and pneumo-thorax.

Dr. K. Douglas Wilkinson said that insufficient attention had been paid to early pneumothorax, high negative intrapleural pressure, and variations in the pulse. Massive collapse is rare. There is no satisfactory explanation of it. Diaphragmatic paralysis is unproved in collapse, and is seen without it. Blocking of bronchus is equally unproved and has special symptoms not seen in these cases. Expiratory fixation of the lung by hypertonicity does not explain complete collapse. He suggested that there existed a spasm of the bronchioles.

Dr. Fortescue Brickdale, by analysis of a large series of cases, showed the value of early aspiration and operation.

Discussed by Dr. W. Gordon, Sir William Hale White, who mentioned the absence of symptoms and the speedy repair of some cases of diaphragmatic injury, by Drs. Buchanan, Charles Miller, Pasteur, who stated the problem of complete collapse and asked what was the cause of it, Stacey Wilson, and Hill Abram.

Sir Clifford Allbutt, assuming that angina pectoris was caused by disease of the envelope of the ascending aorta, or rarely of the heart, divided it into four classes:

1. Acute in rheumatic fever, influenza, &c. Sometimes extremely severe; rarely fatal in rheumatism, more commonly in influenza; to be treated with atropin.
2. Syphilitic; common, often a precursor of aneurysm.
3. Elementary—slight substernal oppression on effort.
4. Ordinary in the elderly, to be treated with continued and rising doses of atropin.

Discussed by Sir R. Douglas Powell, Drs. Cowan, Carey Coombs, McIlwaine (electro-cardiographic evidence), Parkes Weber, John Hay, Ernest Reynolds, Sir A. Garrod, Alex. Morison, most of whom argued for the multiple origin of angina.

Dr. William Collier attacked Dr. Tom Lewis's statement that a healthy heart cannot be overstrained, and related cases in athletes with healthy antecedents.

Dr. Lewis repeated his statement.

Dr. Alexander Morison related cases of advanced heart disease in which pain had been relieved and life prolonged by removal of part of the thoracic wall.

Dr. Cowan showed electro-cardiograms of nodal rhythm with unusual features.

Dr. Morison showed pictures of the microscopic sections of a case of heart-block, in which a calcareous mass, presumably the result of gumma, impinged upon the left bundle.

Drs. Ryffel and Barber stated that acute cases of seborrhoeic eczema show tolerance of alkali, the urine not becoming alkaline under usual doses, and that alkalinization of the urine coincides with the relief of the symptoms due to eczema. The more recent the case the more easily cured. Excretion of acid was a function shared by skin and kidney. The former not yet investigated. The nature of the urinary acid doubtful. Not aceto-acetic, oxybutyric, or lactic.

Dr. A. G. Gibson stated that one-third of all deaths from wounds in a base hospital in England were due to septic phlebitis, of which nearly half were pulmonary. The symptoms were fever, especially rigors, signs in the lungs, and sometimes tenderness over a vein. The prognosis, except for pulmonary cases, was not very unfavourable, but amputation was sometimes requisite.

Dr. G. Hunt described the treatment in oxygen chambers of the results of gas poisoning, especially polycythaemia and nocturnal dyspnoea, and exhibited a model of the chambers used in Cambridge.

Discussed by Drs. Raw and Nixon.

Dr. Gow discussed the view that pulmonary tuberculosis in childhood originates more commonly in the lung than in the glands, corroborating it by a series of observations.

Discussed by Dr. Ryle.

Sir Nestor Tirard stated that the influenza of 1918–19 was distinguished by—

1. The frequency and fatality of pneumonia.
2. The frequency of delirium and coma.
3. Pallor.
4. A bad smell.

Dr. Nathan Raw showed 12-year-old cultures of the three types of tubercle bacilli in which virulence had much diminished.

Dr. Hildred Carlill related a case of hysterical attacks of sleep in which hypnotism failed, though pushed to a point at which the patient would have committed actions naturally abhorrent, and cure was effected by trephining after suggestion.

A very fine series of clinical cases was demonstrated each day between the sessions.

OBSERVATIONS ON A SERIES OF CASES OF HAEMATURIA OF UNUSUAL ORIGIN

By T. I. BENNETT

WITH NOTES ON CYSTOSCOPIC FINDINGS

By C. H. S. FRANKAU

During a period of less than three weeks, in the early part of this year, there came under my observation at a casualty clearing station ten cases whose most prominent symptoms were pyrexia and haematuria. In the following months occasional similar cases were seen, but opportunities for close observation were lacking; six further cases have, however, come to my notice lately.

Several of these were admitted with a diagnosis of 'albuminuria' or 'nephritis', and it is in connexion with war nephritis that they have hitherto been described.

The *Manual of Injuries and Diseases of War*, issued by the Director-General of Medical Services, states, 'In a small but very distinct group the onset is different (i.e. from that of ordinary cases of nephritis), and is characterized by moderate pyrexia, 102° to 103° F., with general aching pains in the back and limbs, with very considerable haematuria; in these cases dropsy is usually slight, or even absent. The haematuria usually subsides in a few days, but is liable to recur, and these recurrences may be associated with a recrudescence of the pyrexia.'

Abercrombie, in the *Journal of the R.A.M.C.* for August, 1916, describes a group of 'lower tract' cases, which agree in their urinary findings, blood-pressure, &c., with the present series; he lays emphasis on the lumbar pain and bladder symptoms, which were not so noticeable in my series, and makes no mention of the shin pains which I found to be the most general cause of distress in my patients.

Moreover, the cystoscopic findings given below are sufficient to show that this is not a disease of the lower urinary tract.

It is hoped in the present paper to draw further attention to this group of cases, which differs remarkably from the main war nephritis group, and which is sufficiently numerous to be important amongst the list of diseases of war.

General Description.

Onset. This is usually sudden, with fever rising to 100° or 102°, the patient complaining of pains in the shins and along the radial border of the forearms; headache is slight; there are often slight pains also in the back.

The respiratory, circulatory, and alimentary systems show only those changes which are common to all mild febrile diseases.

In one case (Case 2) the headache was so severe, and pain in spine so marked, that meningitis could not be excluded on admission; a lumbar puncture was performed and a few drops of normal cerebro-spinal fluid collected; but in no other case were there symptoms or signs of any involvement of the nervous system.

Sometimes on the first day, invariably within a few days, there is marked haematuria; at the same time a slight dysuria may be added to the other symptoms. In several cases it has been the haematuria alone that has led the patient to seek medical aid.

Course of the disease. After a few days the haematuria disappears, though microscopically disintegrated red cells, pus cells, and epithelial débris are still to be found in the urine. But the symptoms persist, lumbar pain and dysuria become more prominent, and the shin pains are often sufficient to prevent sleep.

A labial herpes has several times been observed on about the fifth day. The initial temperature falls to normal, but rises again after, at most, a few days. Often there are sharp, spiky relapses, such as are commonly seen in cases of trench fever; in other cases the pyrexia has developed into a hectic type, with morning remissions.

I have been able to follow one case to its termination; all the others were evacuated still with a little pus and débris in their urine, and still having occasional rises of temperature.

Clinical Pathology of Urine.

In the early stages the urine is the colour of bright blood, and the colour is due to free haemoglobin. For if the urine be allowed to stand in a urine-glass for forty-eight hours, so that the cells sink, the supernatant fluid remains bright red, but clear, showing that the pigment is free from the corpuscles as in cases of haemoglobinuria.

Albumin is present to the extent of about one part per thousand (Esbach).

Considerable deposit accumulates on standing and is found to contain epithelial cells, red blood corpuscles, many of which are disintegrated, a few white corpuscles and pus cells, and a few casts, usually of the granular type. On cultivation of catheter specimens streptococci have several times been found; on other occasions there has been no growth.

Urines taken a few days later usually show no more than a smoky tinge,

but a trace of albumin is still present, and a guaiacum reaction is given, whilst the microscope shows a diminished number of corpuscles, pus cells, and epithelial débris. The recrudescence of haematuria with pyrexia, mentioned in the *Manual of Injuries and Diseases of War*, has been rare in my experience, but occurred in Case 2, where the urine became red again on the fifth day after admission, and the microscope showed an increase in blood cells present. In no case have spirochaetes been found.

Relationship to War Nephritis.

1. *Age.* The age in this series was below the average, whether compared with the average age of soldiers, or the average age of soldiers suffering from war nephritis.

Case 1 was the only man over 35 years of age. The following table is compiled from the statistics given in the third report of the Committee on War Nephritis, in which connexion it must be observed that the figures they quote include certain cases of albuminuria, and cases of haematuria similar to those now under description.

Age.	15–20.	20–25.	25–30.	30–35.	35 and over.
Average age of soldiers (Hume)	10·06	33·06	22·06	13·3	21·4
Nephritis (2,297 cases)	4·04	24·3	21·9	22·52	27·31
Nephritis (100 cases)	5	18	27	23	27
Haematuria (present series)	18·7	31·2	18·7	25	6·2

The contrast is more striking when a comparison is made between the percentage of cases below 25 years of age and those above that figure:

	Below 25 years.	25 years and over.
Average age of soldiers (Hume)	43·1	56·9
Nephritis (2,297 cases)	28·34	71·66
Nephritis (100 cases)	23	77
Haematuria (present series)	49·9	50·1

2. *Pain.* The pains of these haematuria cases had usually an intensity and definition which is seldom, if ever, seen in war nephritis.

In a few, notably Case 6 and Case 11, it was absent, but in many of the other cases the patient would lie awake night after night owing to the shin pains.

Lumbar pain was present in 75 per cent. of the cases, with tenderness and hyperaesthesia to pin-pricks; dysuria was present in seven cases. The attached table summarizes these findings.

Nature of Pain.

Case No.	Dysuria.	Lumbar.	Legs.	Arms.
1	+	—	+	+
2	—	+	+	+
3	—	+	+	+
4	+	+	+	—
5	+	+	+	+
6	—	—	—	—
7	—	+	+	—
8	+	—	+	—
9	—	+	+	+
10	—	+	+	+
11	—	+	—	—
12	+	+	+	—
13	+	+	+	—
14	—	+	+	—
15	—	—	+	—
16	+	+	+	+

3. *Pyrexia.* In war nephritis this indicates bronchitis or some complication; it is seen frequently in the winter cases, much less frequently in the summer ones.

In these haematuria cases it takes, most frequently, the form of sharp, spiky relapses; this is best seen in the charts of Cases 11, 15, and 16.

I am not sure that the hectic type of temperature, developed in Cases 1 and 3, was not due in some measure to the frequent passage of instruments for diagnostic purposes.

4. *Urine.* The copious haematuria with evidence of dissolution of corpuscles is a phenomenon unlike anything seen in ordinary war nephritis. The clear, blood-red urine forms a striking picture, in marked contrast to that of the urine of war nephritis, which has at most a smoky tinge. It is true that a few granular casts have not infrequently been seen, but they form a very small proportion of the total cellular content, which consists at first of epithelial débris and disintegrated blood cells, and later of débris and pus.

The albumin present was never in excess of 1·5 parts per 1,000, and seldom reached this amount; it was, in fact, in accordance with the degree of corpuscular destruction present, and never resembled those massive quantities of albumin which are so striking a feature of war nephritis in its early stages.

5. *Cystoscopic appearances.* In each of the four cases examined with the cystoscope the signs were those associated with a pyelitis or pyelonephritis of infective origin. The intensity of the inflammation and oedema around the ureteric orifices was most marked in those cases which were examined early; those examined at a later stage showed much less marked signs.

A number of cases of 'war nephritis' were examined in 1916, when no cystoscopic abnormality was found: these cases would therefore appear to belong to a definite type differing from the cases normally seen during the war.

6. *Oedema.* In no case have I been able to find definite evidence, whether in the face, the back, or the legs, of oedema. Cases 4, 7, 13, and 14 gave a

doubtful history of swelling of the face or legs before admission, but nothing definite could ever be demonstrated.

7. *Dyspnoea.* The absence of dyspnoea, either nocturnal or on exertion, is a feature of these cases which, however difficult it may be to reduce to scientific terms, is very different from the clinical manifestations of war nephritis.

8. *Output of Urine.* The difficulties of obtaining accurate measurements, especially in a busy casualty clearing station, are so great that I publish these findings with reserve; but it will be seen that certain cases had polyuria, and in none was there anything like suppression of urine.

Day after Admission:	1	2	3	4	5	6	7	8	9	10	Day of Disease when admitted.
Case No.											
11	30	38	27	26	42	33	27	25	32	44	?1
12	14*	56	57	51	64	64	77	54	62	38	4
13	16*	38	35	32	55	42	54	64	62	42	13
14	18*	60	59	54	80	52	54	42	46	42	4
15	12*	56	53	54	94	51	50	55	74	74	4
16	50	31	30	44	54	46	58	20?	33	36	1
3	14*	34	44	36	50	88	111	54	72		3
5	25	24	32	28	45	20	61	32			3
7	74	70	74								3
8	36	50	48	35							2

Measurements in fluid ounces.

* Indicates urine for 12 hours only.

9. *Blood-pressure.* In war nephritis a raised blood-pressure is almost invariably found in the early stages of the disease; in the present series the blood-pressure was normal in all save three cases.

I have been unable to get statistics for this finding in any large series of nephritis cases, and the following table is compiled from ten cases under my care recently. B. P. was in all cases taken by the auscultatory method with a Tycos sphygmomanometer.

	Total Cases.	Average B.P.	Below 100.	100–130.	130–150.	Above 150.
Nephritis	10	147	Nil	3	3	4
Haematuria	16	114	1	13	2	Nil

Reviewing these findings as a whole, it becomes apparent that the inclusion of these cases amongst those of war nephritis is justified only by the presence of occasional casts in the urine. In many cases these casts were not present in greater quantity than those seen in the urines of apparently healthy soldiers with albuminuria discovered in the course of routine examination.

But in one case at least they were, at a late stage of the disease, present in larger quantities. Case 16, after having been four weeks under observation, showed renal epithelial cells, epithelial, granular, and hyaline casts, and pus cells in his urine, whereas on admission he had had but scanty granular casts with large numbers of red blood corpuscles.

The secondary cystitis demonstrated by the cystoscope suggests that some

toxic substance is descending the ureter, and it is hardly to be expected that such a substance will leave the kidney itself untouched.

But the picture is very different from that of war nephritis as a whole.

Relationship to Trench Fever.

If examination of the urine had been omitted, many of these cases would have been diagnosed as trench fever. In spite of the enormous amount of work which has been done on the latter disease, we remain without any certain means of diagnosing it, short of inoculation experiments on man. Signs, such as nystagmus, splenic enlargement, and the ripple reflex, however great their clinical interest, are of little diagnostic assistance. One is left with a symptom-complex and a characteristic temperature chart; both of these are also features of these cases of haematuria.

The recent discovery that trench fever may be transmitted by the dried deposit of centrifugalized urine from infected cases is very suggestive, and it is hoped shortly to begin experiments to determine whether the same phenomenon can be produced from the urine of haematuria cases.

Cases 12 and 15 were lads of the same section of one battalion; they did not actually share one another's blankets, but had occupied the same dug-out, and at the time of onset of symptoms were together on a course of instruction, sleeping in a hut at a musketry school. It was fine midsummer weather when they were taken ill, but cases of trench fever were not uncommon.

Tabulated Findings.

Case No.	Age.	Blood Pressure.		Oedema.	Day of Onset of Haematuria.	Diagnosis on Admission.
		Diastolic.	Systolic.			
1	39	70	108	—	2	? Haematuria
2	20	85	110	—	5	P.U.O.
3	32	90	130	—	?5	Albuminuria
4	26	80	105	?	?	Haematuria
5	29	60	80	—	3	P.U.O.
6	31	70	110	—	?1	P.U.O.
7	27	85	120	?	1	Haematuria
8	30	80	110	—	2	N.Y.D. albuminuria
9	30	80	120	—	?1	? Nephritis
10	30	70	120	—	2	P.U.O.
11	21	100	120	—	?1	Dental abscess
12	18	80	134	—	1	? Nephritis
13	20	85	105	?	?10	Acute nephritis
14	19	78	115	?	1	Albuminuria
15	19	90	138	—	1	? Nephritis
16	23	70	105	—	1	Haematuria, ? cause

Case 1. Pte. A. R., M.C. Coy., aged 39. Admitted 19.2.18 for '? haematuria'.

On 10.2.18 was living in an uncomfortable but dry dug-out, just behind trenches; perfectly well.

11.2.18–14.2.18. In good billets in a small town; evening of 14th had a hot bath.

15.2.18. Woke up with headache and pains in limbs. 16th. Pains in

limbs, especially shins, worse; slight dysuria, observed urine to be 'dark chocolate' colour. Reported sick, given M. sod. sal. and M. alba t.d.s.

19.2.18. To C.C.S. from Field Ambulance with note that urine had contained blood. On admission complained of shin pain and pain along radial border of forearm; slight pain in penis and groin on micturition. No abnormal physical signs in chest; no oedema; no respiratory symptoms; blood-pressure: diastolic 70, systolic 108. No blood obvious to naked eye in urine, but strong positive guaiacum test. Microscopically many red cells, epithelial cells, a few granular casts. No spirochaetes, no tubercle bacilli.

28th. Looks well, but arm and leg pains continue; pyrexia (99°) morning and evening.

6th. Pyrexia increased; sleepless from arm and leg pains. Urine still gives positive reaction for albumin.

Report on cystoscopy. 'Easy. 16 oz. distension. Normal bladder except possible slight injection of mucous membrane at openings of ureters, hardly noticeable. Effluxes normal.'

11th. Evacuated to Base, symptoms unimproved.

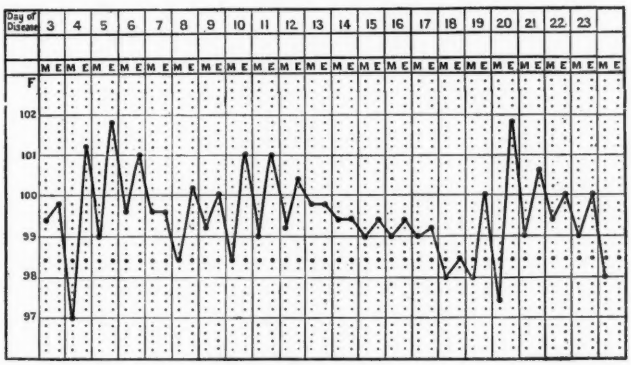
Day of Disease
3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E
F
102
101
100
99
98
97

FIG. 1.

Case 2. Pte. J. M., S. Lancs. Regt., aged 20. Admitted 25.2.18 for 'P.U.O.'

21.2.18. Had been billeted for fourteen days in good billets in a small town. Quite well, but began to have slight pains and stiffness in his legs.

24.2.18. In afternoon was suddenly seized with intense backache, dizziness, pains in neck, arms, and legs. Taken to Ambulance. Given aspirin.

25.2.18. To C.C.S., complaining of intense pain in spine, so that breathing was painful. Less acute pains in limbs, especially arms. T. 102°, P. 116, R. 20. No pulmonary symptoms; a few faint rhonchi heard at r. base. No oedema. Tongue furred, white. Much blood in urine. Blood-pressure: diastolic 85, systolic 110. Lumbar puncture performed under light anaesthesia—a few drops of limpid fluid obtained, sterile on culture and normal on microscopic examination. Urine on microscopic examination showed a few epithelial casts, a few red corpuscles, pus cells, and epithelial cells. Much débris. No spirochaetes. Catheter specimen showed a few Gram-positive cocci on culture.

28.2.18. Pains much better. T. normal.

2.3.18. Recurrent pyrexia.

5.3.18. *Report on cystoscopy.* 'Some slight general congestion. Two small patches of submucous haemorrhage, one high up in upper segment to r. side, and one just above opening of l. ureter. All around both ureteric orifices congestion—most marked on l. side, where there was oedema and exudate. Effluxes equal and normal.'

10.8.18. Much better. Apyrexial; sent to Base. No blood or albumin discoverable in urine.

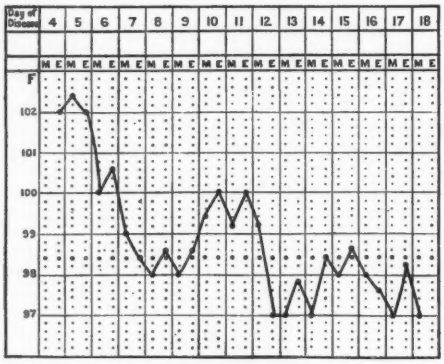

FIG. 2.

Case 3. Pte. F. A. P., M.G. Coy., aged 32. Admitted 25.2.18 for 'albuminuria'.

19.2.18. Went into billets after fourteen days in concrete cellar near trenches. Quite well.

23.2.18. Woke up with headache, pains in limbs, and weakness on walking. Returned to bed until taken to Ambulance.

24.2.18. At Ambulance. T. 100·4°. Arms felt 'dead'.

25.2.18. To C.C.S. Pains in head and legs and occasionally in back. No oedema. No abnormal physical signs. No dysuria. Urine bright red. Blood-pressure: diastolic 90, systolic 130. On microscopic examination urine showed granular casts, some red cells, a few pus cells. No spirochaetes. On culture a few Gram-positive cocci.

1.3.18. Recurrent pyrexia. Trace of blood still in urine. Urine volume normal, 50 oz. daily. Cystoscopy not attempted as meatus was unusually small. Symptoms better.

8.3.18. Symptoms continue. Evening, pyrexia.

10.3.18. To Base.

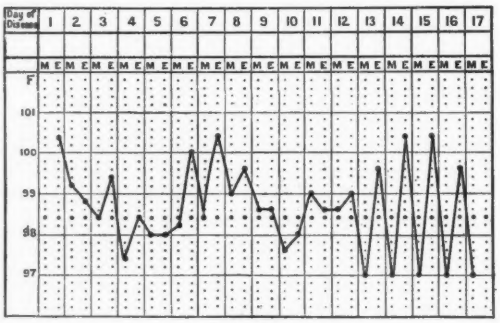

FIG. 3.

Case 4. Pte. A. C. H., K.L. Regt., aged 26. Admitted 25.2.18 for 'haematuria'.

10.2.18. On leaving trenches he reported sick on account of 'swelling of the thighs'. This was apparently a local trouble due to trench boots; he remained

in a barn, off duty, for four days, in a small town; then marched with twenty other men suffering from minor ailments to other billets seven miles distant.

18.2.18. Began to have pains in r. lumbar region and in legs; never pain in arms. Remained off duty.

25.2.18. On admission, pains in legs; slight tenderness over r. loin; no trace of oedema; no abnormal signs or symptoms in chest. Marked haematuria. Blood-pressure: diastolic 80, systolic 105.

28.2.18. Temperature irregular. Report on urine: granular and blood casts, red blood corpuscles, pus, and epithelium. No spirochaetes. Much débris. Urine sterile on culture of catheter specimen.

3.3.18. Urine clearer to naked eye. R.B.C., a few leucocytes, and scanty casts still present microscopically.

5.3.18. Cystoscopy: 'Cystoscope passed easily, 12 oz. distension. Slight general congestion. Two small patches of confluent submucous haemorrhage to be seen above and behind r. ureteric orifice, similar to C. (Case 5), but less marked. Small patch of congestion in front of r. ureteric orifice. L. side normal. Effluxes normal.'

7.3.18. Temperature normal. Pains in r. loin and legs continue, especially at night.

10.3.18. Temperature rose sharply to 104·8°.

11.3.18. Temperature fallen to normal; no marked change in symptoms Blood culture taken at height of pyrexia—sterile.

15.3.18. Temperature normal three days. Evacuated to Base.

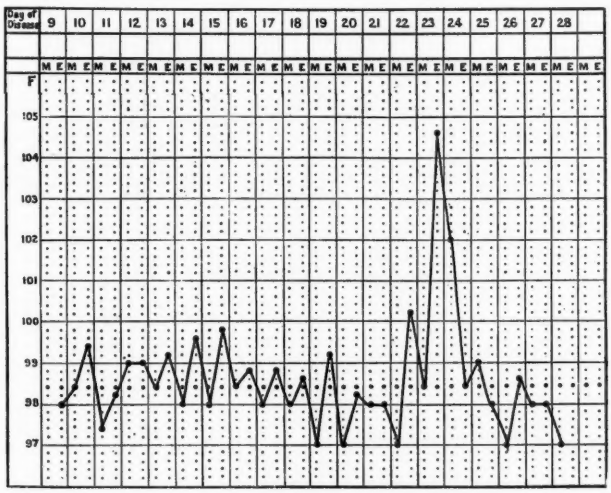

FIG. 4.

Case 5. Pte. F. C., R.W. Fus., aged 29. Admitted 4.3.18 for 'P.U.O.'

1.3.18. Pains in thighs, shins, and lumbar region. Reported sick.

2.3.18. T. 102°, evacuated to Ambulance.

3.3.18. Pains continue. On passing urine in the morning observed that it was 'bright red'.

4.3.18. Admitted C.C.S. T. 99°, P. 56. Faint labial herpes. No oedema. No abnormal signs in chest. Complains of severe pains in shins and along radial border of forearm. A little pain at end of micturition. Urine bright red; deposit contains many red corpuscles, a few pus cells, granular casts, epithelial débris. Blood-pressure: diastolic 60, systolic 80.

5.3.18. *Cystoscopy.* 'Would not permit passage of cystoscope without light anaesthesia, C_2E_3. Distension 14 oz. Whole bladder-wall showed congestion with distension of vessels—most marked in upper segment of bladder and above and behind r. ureteric orifice, where the appearance was that of a submucous haemorrhage. In front of either ureteric orifice there was a fairly marked injection of mucous membrane, most marked on r. side, where there was also oedema. Effluxes increased in frequency, and smoky.'

8.3.18. Temperature normal. Symptoms persist; urine faintly smoky to naked eye. Daily urine 30–40 oz.

10.3.18. Recurrent pyrexia.

12.3.18. To Base, unimproved.

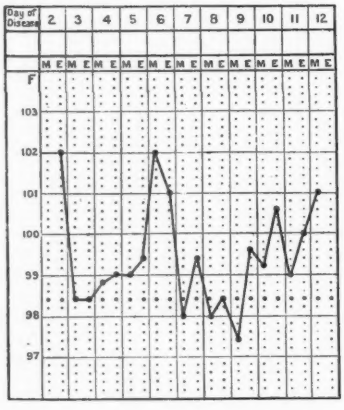

FIG. 5.

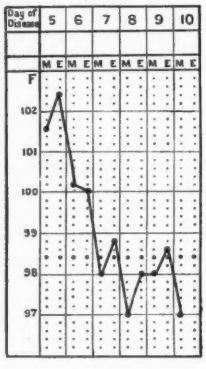

FIG. 6.

Case 6. Gnr. J. S., Siege Battery, R.G.A., aged 31. Admitted 5.3.18 for 'P.U.O.'

26.2.18. Billeted in barn in a small village; had a cold, ached all over; at the same time noticed his urine 'brown, like coffee'; next day it was clear again. Apparently recovered completely.

About 1.3.18 observed weakness and tiredness after walking; very slight occasional headaches; no other complaint at all except that urine had again become brown. Reported sick; temperature found elevated, sent to Ambulance.

5.3.18. Admitted C.C.S. Whilst in bed has no symptoms whatever. Chest shows no abnormality. No oedema. Tongue clean. No tenderness or pain night or day. No urinary symptoms, except colour of urine. Blood-pressure: diastolic 70, systolic 110.

8.3.18. Report on urine (non-catheter specimen): 'Abundant chocolate-brown deposit of haemoglobin. R.B.C. not very numerous. Scanty leucocytes. No casts found.' Urine volume 50 oz. and upwards.

10.3.18. Still no symptoms, but haemoglobin and albumin still in urine, though colour is much lighter. To Base.

Case 7. Sgt. R. D., R.W. Kents, aged 27. Admitted 7.3.18 for 'haematuria'.

1.3.18. Was in support trenches. Quite well.

4.3.18. Reported sick on account of pains in head, and because he had noticed that his urine had that day become red.

5.3.18. Head clearer. Pains in shins, ankles, and behind knee-joints. Urine unchanged and unusually free, micturition about every two hours, day and night.

6.3.18. Urine clearer, but very frequent. Legs unchanged but 'slightly swollen in calf and shin-bone'; his comrades could observe this. At night pains in head and legs kept him awake.

7.3.18. To Ambulance and C.C.S. On admission—pains in shins; head 'not quite clear'; no pain in body or arms. Slight cough. Tongue—slight brown fur. No herpes. Eyes clear. Slight dysuria; urine smoky. No abnormal signs in chest. No trace of oedema. Blood-pressure: diastolic 85, systolic 120.

8.3.18. Sleepless on account of leg pains. Sharp lumbar pain and headache. Tongue lightly furred. Shins very tender to pressure, no oedema. Lumbar tenderness and ? tender over bladder. No dysuria, urine 70 ozs. daily. Slight cardiac dilatation. T. 102°, pulse 80. Faint sticky râles in chest. Urine shows abundant granular casts, red corpuscles, and leucocytes.

10.3.18. Urine on culture of catheter specimen gave growth of streptococci and a few Gram + bacilli.

11.3.18. To Base, unimproved.

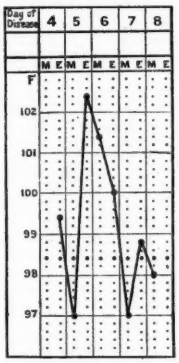

FIG. 7.

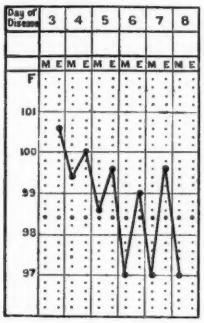

FIG. 8.

Case 8. Pte. F. G., Queen's Regt., aged 30. Admitted 7.3.18 for 'N.Y.D. albuminuria'.

2.3.18. In trenches; quite well.

5.3.18. Frontal headaches and aching all over at night.

6.3.18. Still feeling bad; fainted whilst marching up to front line trenches; managed to reach a bivouac, where he remained all night; no dysuria, but noticed in afternoon that his urine was red.

7.3.18. Reported sick; symptoms unchanged. To Ambulance and C.C.S.

8.3.18. Pains in head and limbs; knuckles of r. hand swollen and tender (a long-standing condition, probably traumatic). No abnormal signs in chest, no lumbar pain. Abdomen tender on palpating kidneys and bladder. Pain in groin after micturition. Tongue clean, no herpes. Blood-pressure: diastolic 80, systolic 110.

10.3.18. Urine 30–50 oz. daily. Microscopically contains abundant granular casts. Red blood corpuscles and leucocytes also present. To naked eye is now almost normal.

12.3.18. Continued evening rise of temperature. To Base, unimproved.

Case 9. Pte. F. R., K.L. Regt., aged 30. Admitted 19.3.18 for '? Nephritis'.

14.3.18. Headache, pains in back and arms, and in calves of legs, which 'felt tight'. Could not sleep. No dysuria or polyuria, but noticed that urine was 'like cocoa'. Reported sick, found to have pyrexia (?102°), sent to bed.

15.3.18. No change. Temperature fell, but rose in evening.

16th–18th. Swinging temperature.

19.3.18. To C.C.S. Rather pale. Slight frontal headache, pains in back and shoulders, legs 'weak'. Tenderness in loins and on deep palpation of iliac fossa, also over lower cervical spine. No abnormal signs in chest. Tongue light-brown furring. Blood pressure: diastolic 80, systolic 120. No oedema. No dysuria, urine smoky.

20.3.18. Report on urine: '"Smoky", contains blood and albumin. No indican. Heavy urates content. Centrifugalized deposit—much débris. Disorganized haemoglobin. Many pus cells and disintegrated reds. A few granular casts. No T.B. bacilli.'

22.3.18. Slight dysuria. Urine 30 oz. daily. No frequency. Pyrexia continued. Pains in back and legs. Tongue furred.

24.3.18. Temperature normal. To Base, unimproved in symptoms.

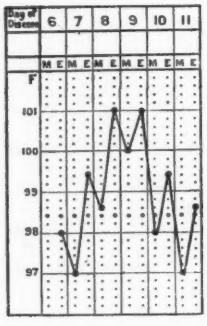

FIG. 9.

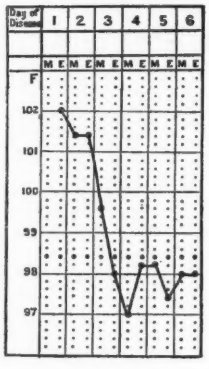

FIG. 10.

Case 10. Pte. F.T., S.W.B., aged 20. Admitted 19.3.18 for 'P.U.O.'.

19.3.18. Woke up quite well, but whilst on the march had to fall out on account of pains in head and legs. Reported sick, unable to carry his pack. To Ambulance and C.C.S. On admission stated that his urine was normal, but shortly afterwards, at latrine, he observed it to be 'coffee-colour'. Next morning it was bright blood-coloured. Pains in shins, elbow-joints, and along radial border of forearms. Slight lumbar pains. No oedema; no abnormal signs in chest. Blood-pressure: diastolic 70, systolic 120.

20.3.18. Report on urine: 'Distinctly acid. Blood and albumin present. No sugar or indican. Heavy deposit on centrifugalizing, supernatant fluid blood-tinged, indicating haemoglobinuria. Deposit shows much débris haematogenous in origin. Very many reds, chiefly distorted. Leucocytes in proportion. Many squamous epithelial cells. Very occasional granular casts. No spirochaetes. No T.B. bacilli.'

21.3.18. Sleepless from shin pains, faint labial herpes. Pain in back gone. Urine clearer. Frequency but no dysuria.

23.3.18. Temperature normal. Report on urine: 'Almost neutral. A trace of albumin. No blood, sugar, or indican. Centrifugalized deposit—scanty, a few pus cells and squamous and pyriform urinary epithelial cells. No casts.'

24.3.18. Much better. Allowed up for an hour.

25.3.18. Evacuated to Base.

Case 11. Air Mechanic F., R.A.F., aged 21. Admitted 12.6.18. for 'dental abscess'. Patient came sick on account of a swollen upper lip. Two septic

incisor roots were at once extracted and a dental abscess drained. On the same day routine examination of urine revealed bright haematuria. Urinary deposit contained red cells, epithelial débris, and a few pus cells; supernatant fluid remained clear, bright red after 48 hours. B.P. 120–100. No pains anywhere save in mouth.

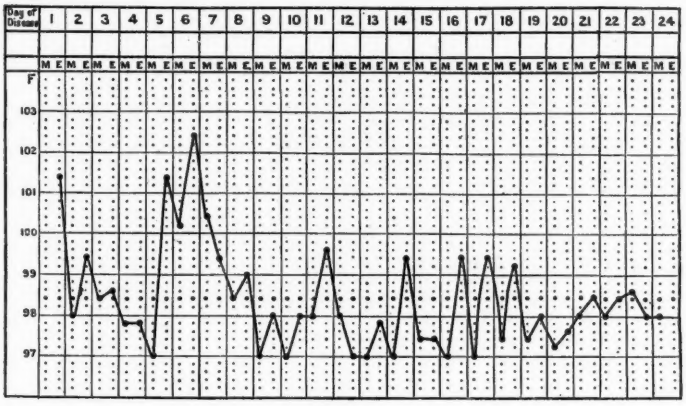

FIG. 11.

16.6.18. Recurrent pyrexia. No pains anywhere. Mouth clean, urine light red after having been clear on 15th. Crenated R.B.C. and pus cells present.

22.6.18. Recurrent pyrexia. Urine clear; a few pus cells and epithelial cells. R.B.C. still present. Very few granular casts.

28.6.18. Slight definite lumbar pain. Pyrexia. No blood naked eye, but a little débris and a few pus cells found.

4.7.18. Apyrexial for a week. No symptoms. To duty.

Case 12. Pte. A. E., Suffolks, aged $18\frac{10}{12}$. Admitted 2.8.18 for '? nephritis'.

31.7.18. At a school of instruction noticed frequency of urine and dysuria; complained of strange feelings 'in his stomach'. Urine observed 'dark brown'.

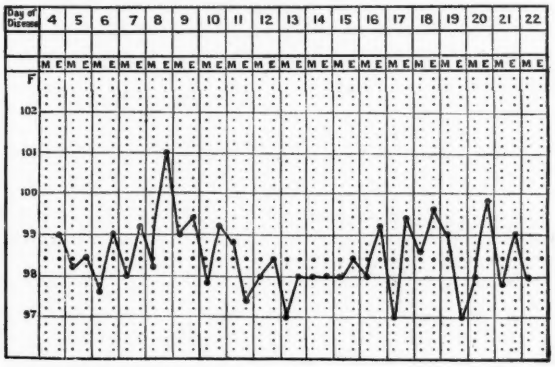

FIG. 12.

3.8.18. Frequency and dysuria unchanged. Otherwise feels well. Very slight abdominal tenderness. Tender in r. loin, hyperaesthetic to pin-pricks in

same region. Oedema nil. Chest nil. Bright blood in urine. Pathologist reports: 'Urine contains red blood corpuscles, fairly numerous leucocytes. Granular casts in small number.'

11.8.18. Slight pain in r. loin.
15.8.18. Up. Slight dysuria.
17.8.18. Complains of sharp pains in shins and back.
28.8.18. Much nocturnal backache. To Base.

Case 13. Gnr. W. B., R.F.A., aged 20. Admitted 6.8.18 for 'acute nephritis'.

23.7.18. Headache and malaise; states that face and legs became swollen. Remained off duty seven days.
3.8.18. Pain in penis, urine red.
4.8.18. Pain in head, back, and thighs. Dysuria and nocturnal frequency.

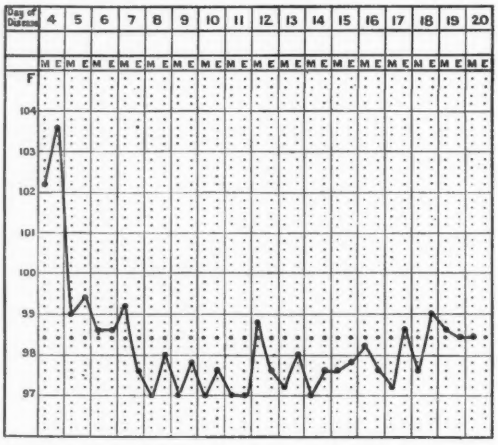

FIG. 13.

6.8.18. Symptoms as above. Sleepless on account of frequency of urine. Lumbar tenderness and cutanous hyperaesthesia. No oedema or dyspnoea. Bright blood in urine. Microscopically many R.B.C., leucocytes, a few granular casts.

8.8.18. No pains, save aching of ankles.
12.8.18. Nocturnal aching of legs and fingers.
15.8.18. Up. Feels well.
23.8.18. Occasional pains in knees. To Base.

Case 14. Pte. E. S., Welsh Regt., aged 19. Admitted 4.8.18 for 'albuminurias.

1.8.18. Coming off a march passed blood in urine. During night had pain in back and stomach with dysuria.

4.8.18. Blood in urine diminished, but still quite bright. States face was swollen yesterday, no trace of oedema demonstrable. Abdomen tender over bladder. Lumbar tenderness on both sides. Cardiac arrhythmia, old mitral lesion.

6.8.18. Urine smoky; microscopically contains spermatozoa, leucocytes, mucous shreds, a few disintegrated R.B.C.

15.8.18. Up daily. Slight lumbar pain.
21.8.18. To Base.

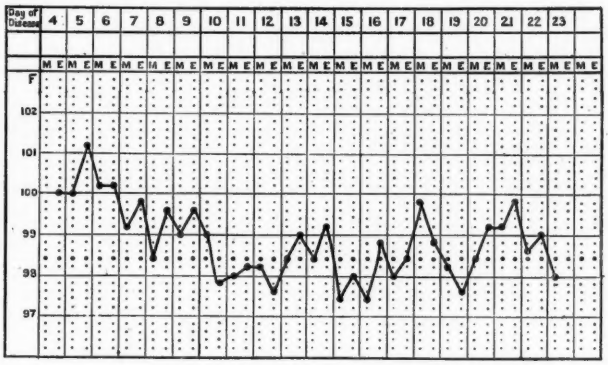
Day of Disease
4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E
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FIG. 14.

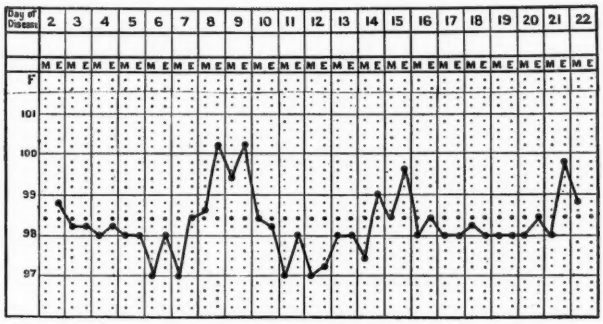

FIG. 15.

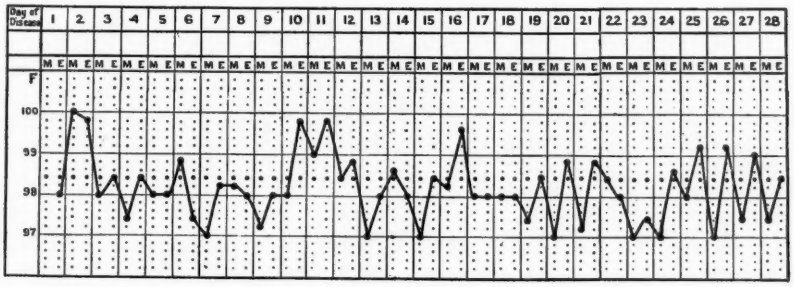

FIG. 16.

Case 15. Pte. W. E., Suffolks, aged 19. Admitted 3.8.18 for '? nephritis'.

31.7.18. Fell out on the march. Noticed blood in urine.

1.8.18. Went sick on account of blood; feeling well, no frequency or pain of any sort.

3.8.18. Slight nausea only symptom. Tongue lightly furred. Chest nil. Oedema absent. No tenderness. Bright blood in urine; microscopically very many R.B.C. Many leucocytes. Many granular casts.

8.8.18. Recurrent pyrexia. Pains in knees and ankles. Lumbar cutaneous hyperaesthesia, but no tenderness or pain.

17.8.18. To Base. No symptoms.

Case 16. Gnr. T. E. H., R.F.A., aged 23. Admitted 11.8.18 for 'haematuria'. On admission had had pain and frequency of micturition for twelve hours. Headache, lumbar pain. No oedema. Urine bright red. Pathologist reports: 'R.B.C., pus cells, a few granular casts, and renal epithelial cells present.'

21.8.18. Pains in back, shins, and radial border of forearms. Recurrence of pyrexia.

28.8.18. Better. Up daily.

7.9.18. Pyrexia and pain in back and legs. No visible blood. Pathologist reports: 'Pus cells, renal epithelial cells, epithelial, granular, and hyaline casts present.'

12.9.18. To Base.

THE ACTION OF CHLORINE, ETC., ON THE BRONCHI

REPORT TO THE CHEMICAL WARFARE COMMITTEE

By J. A. GUNN

(From the Department of Pharmacology, University Museum, Oxford)

With Plates 2 and 3

THE Chemical Warfare Committee suggested to me the following subjects for investigation: (1) the effect of chlorine inhalation on the calibre of the bronchi and (2) the utility of drugs that could be used to counteract whatever effect chlorine was found to produce. I have not thought it necessary in this report to deal with the literature of the subject or to do more than give a summary of my observations. It is not a matter of great difficulty to determine the action on the bronchi of drugs that can be administered intravenously, especially if they act peripherally; and various methods devised for this purpose are in ordinary use. The difficulties multiply when one begins to apply those methods to the investigation of a gas like chlorine, and some of those difficulties are mentioned in the report. Such methods as I was able to devise for obtaining some indication of the effects of known concentrations of the gas are not entirely free from objection, but I have described in some detail those I found most reliable because it is possible that, for investigating the action of gases that do not corrode metal or rubber, they could be applied with such slight modification as would remove the objections mentioned.

A. *Methods of recording Changes in the Calibre of the Bronchi.*

Of the various methods that have been employed for recording changes in the calibre of the bronchi, none are very direct, and most of them depend upon the fact that, with constant force used to expand the lungs—e.g. by positive artificial respiration through the trachea—the amount of excursion of the lungs varies with the sectional area of the lumen of the bronchioles. The amplitude of the lung movement can be graphically recorded. I have used chiefly the following methods. The experiments were made on anaesthetized rabbits or decerebrated cats. Artificial respiration was carried out by Brodie's pump, which delivers a sufficiently regular blast of air, that could be warmed or charged with a volatile anaesthetic as required.

The following device for recording the expansion of the lungs was found after many experiments to be most successful (see Diagram I). A circular opening was made in the chest just above the diaphragm. The opening was about half an inch in diameter, and haemorrhage was prevented by ligatures round the ribs and sternum where required. An inverted thistle-funnel was tied into this opening. The exit tube of the thistle-funnel was connected with a tambour, C, with a T-tube, B, intervening. The tambour was covered with a slack membrane (thin rubber loosely tied). The T-tube had a clip, D, on the tubing attached to the vertical limb, by means of which the excursion could be regulated to a convenient size. By this method one really measures the 'jerk' imparted to the tambour by the expanding lung. The actual volume of the lung is not

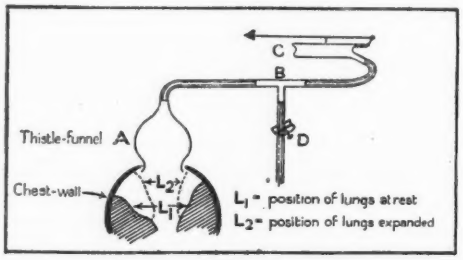

DIAGRAM I.

recorded, as the system is not closed; having an escape at D, one avoids any excessive positive pressure on the outer surface of the lung. With constant artificial respiration, the excursion of the tambour is constant. If the bronchioles dilate the lung expands farther and faster and the 'jerk' is increased; contrariwise, when the bronchioles contract. Fig. 1, Plate 2, illustrates the record one obtains, showing the regularity of the normal excursion and the marked reduction produced by intravenous injections of a minute dose of ergamine. This use of a thistle-funnel instead of a cannula in the pleural cavity is important. I have tried the various kinds of cannulae in use and none of them are reliable. They may give misleading tracings by the mouth of the cannula being blocked by the expanding lung. This cannot happen with a thistle-funnel unless one uses an excessive expansion of the lung. The transparency of the funnel also allows one to see to some extent what is actually happening to the lung.

B. *Method of introducing a Known Concentration of Gas into the Air respired.*

The problem was how to introduce into the lungs at will a known concentration of gas, while keeping constant the blast that entered the tracheal cannula. One of the chief difficulties is that one cannot pass chlorine through a metal cylinder without injuring the cylinder, nor can one pass it through anything but a small length of rubber tubing, as the latter takes up the chlorine.

Diagram II illustrates the method adopted. The air pumped by the Brodie's pump was made to pass through a carboy before entering the trachea. By means of the connexions shown, while the normal tracing was being taken the air passed along the route A, B, C, E. When the action of the gas was to be tested the rubber tube C was closed with a clip and, by opening two other clips, the air passed through the other limbs of the Y-tubes B and E, between which was a glass tube D full of pure chlorine. This chlorine was then driven into the carboy and so into the lungs. By keeping the width of the glass and rubber tubing the same throughout, it was found by experiment (the tube D in this case containing air only) that no change in the lung excursion was mechanically produced by changing from C to D. The carboy had a volume of 45 litres, and different

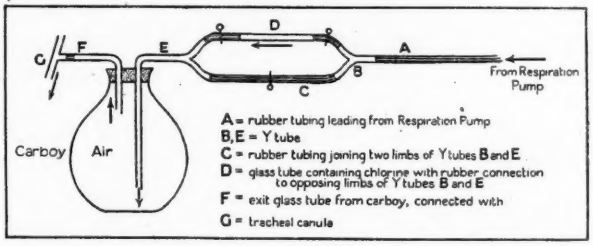
G
F
E
D
A
B
C
From Respiration Pump
Carboy
Air
A = rubber tubing leading from Respiration Pump
B,E = Y tube
C = rubber tubing joining two limbs of Y tubes B and E
D = glass tube containing chlorine with rubber connection to opposing limbs of Y tubes B and E
F = exit glass tube from carboy, connected with
G = tracheal canula

DIAGRAM II.

concentrations of chlorine were obtained by cutting different lengths of tube D, the capacity of which could of course be easily measured. In the apparatus as set up, the chlorine passed through glass with the exception of about 1½ inches of rubber tubing. The rhythmic pumping served to mix the chlorine in the carboy before it reached the trachea. The concentration of chlorine rapidly fell as more air was pumped through the carboy, but it is difficult to devise for such experiments any method by which this can be avoided. The chief drawback of this method is that, when the air is pumped through a large carboy on its way to the trachea, this reservoir tends to convert an intermittent into a constant blast of air. It was possible to prevent this to a sufficient degree to get some satisfactory experiments, but in many cases, owing to insufficient ventilation of the lungs, natural respiration began in spite of artificial respiration, in which case the tracing was too irregular to be satisfactory. However, by controlling the results with the following method, one could obtain a sufficiently certain indication of the effects of chlorine on the bronchi.

C. *Control Method.*

The results of experiments obtained by the above method were compared with those obtained in the following way (see Diagram III).

The animal breathed naturally. The tracheal cannula was provided with an expiratory valve which allowed air to be breathed out but not inspired. The air

was inspired through a carboy as figured. A normal tracing was first taken, and then by means of a glass syringe a known volume of chlorine was injected into the carboy and the animal then breathed air containing a known concentration of chlorine instead of pure air. The effect on the respiration was determined by a respiratory stethograph, and the effect on the bronchi could to some extent be estimated by comparing the stethograph record with a record which was simultaneously taken of the intrapleural pressure.

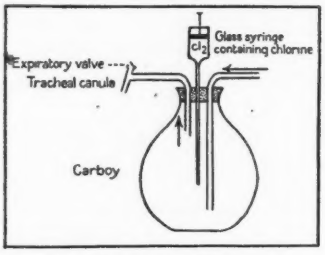

DIAGRAM III.

D. Action of Chlorine on the Bronchi.

It was theoretically probable that any effect exerted by chlorine on the musculature of the bronchi would be a reflex one, and in any case the possibility of this occurring had to be allowed for. It was necessary, therefore, that the excitability of the respiratory centre should be maintained in a condition as normal as possible. In all the experiments on cats, the animals were decerebrated by Sherrington's method. After decerebration normal respiration is resumed, and the effect of chlorine was not tried until at least half an hour after decerebration, by which time there would be eliminated most of the anaesthetic (chloroform) which had been used before decerebration. Shortly after decerebration, artificial respiration was begun, and after a short time normal respiration ceased, but would immediately begin if artificial respiration were interrupted. The animals were therefore in good condition as regards the activity of the respiratory centre and it was reasonable to assume that reflex effects on the bronchi were elicitable. In rabbits urethane was tried as an anaesthetic. Brodie and Dixon have stated that it interferes with bronchial reactions, preventing the exhibition of constrictor and dilator effects by drugs which show these effects in the absence of urethane. This I also found, and abandoned urethane as an anaesthetic. In rabbits I therefore used chloroform-ether until the operation was over, and then ether alone. Fig. 2, Plate 3, shows the absence of effect of ergamine on the bronchi of a rabbit anaesthetized by urethane (cf. Fig. 1). After experiments with many drugs I found ergamine the most certain in its action on the bronchi, and I therefore employed it in testing various methods, &c. I found that chlorine in concentrations of 1 in 5,000 to 1 in 1,000 produces a short-lasting reflex constriction of the bronchi. This occurs immediately it is inhaled, and does not last more than

a minute or so. Fig. 3 shows the effect of chlorine, 1 in 2,000, on the bronchi and blood-pressure of a decerebrated cat. The effects on the bronchi were determined by artificial respiration and the thistle-funnel method of recording. There was a brief broncho-constriction, lasting about one minute, accompanied by a fall of blood-pressure.

Fig. 4 shows the effect of the same concentration of chlorine on a rabbit, breathing naturally. A record was taken of the respiratory movements by stethograph, and of the intrapleural pressure and of the blood-pressure. The inhalation of chlorine produced a diminution of the amplitude of the movements, the inspiratory movement being increased and the expiratory diminished. But coincident with this the positive as well as the negative pressure in the thorax was increased. This is typical of what happens when the bronchi are constricted (e.g. in spasmodic asthma), the chest tending to become fixed in the inspiratory position. Owing to the constriction of the bronchi, the less vigorous expiratory effort is unable to empty the lungs and the excursion of the chest in expiration is lessened. But the actual expiratory effort is usually increased, so that though the expiratory *movement* is diminished, the positive intrathoracic *pressure* is increased by expiration. There can be little doubt that the tracing therefore indicates a short-lasting bronchial constriction. The respiration is simultaneously quickened. The acceleration of respiration lasts for a much longer period than the bronchial constriction As has been noted by other observers, the blood-pressure falls.

Generally, the results of experiments with chlorine have gone to show that inhalation of 1 in 5,000 up to 1 in 1,000 produces an increased rate of respiration with a transient broncho-constriction. This broncho-constriction is produced reflexly by the first contact of the irritant vapour with the bronchial mucous membrane. It lasts such a short time that therapeutic measures to combat it would be unavailing. A subsequent sudden increase in the concentration of the gas may produce another transient reflex broncho-constriction. Continued inhalation of the gas produces thereafter an apparent slight and gradual broncho-constriction, but from histological observations it appears probable that this is due rather to oedema of the bronchial mucous membrane than to contraction of the bronchial muscle.

It is perhaps well to keep in mind that reflex effects arising from irritation of the upper air-passages are excluded in these experiments. It is theoretically probable that irritation of the nasal and laryngeal mucous membranes will produce more immediate and possibly more intense reflex effects on the bronchi than will irritation of the trachea; for the sentinel posted in the latter region challenges the enemy gas too late.

The Action of some Drugs on the Bronchi.

In the course of these experiments, while various methods were being tried, a number of observations were made on the action of drugs. Of these observations perhaps the following have some bearing on the present line of investigation and

may be of some assistance to others engaged on it. Of the drugs I tried—and I tried most of those which are reputed to possess this action—the most certain broncho-constrictor is *ergamine*, the action of which has been fully described by Dale. It has this advantage, that it produces a fall of blood-pressure in the cat and a rise in the rabbit, so that the fact that the bronchial changes recorded are independent of vascular changes in the lung can be arrived at without other elaborate proof. If the dose employed be small, e.g. about 0·1 or 0·2. mg. per kilo, the effect can be repeated several times. If the dose be much above that, the bronchi remain constricted during the usual time of an experiment.

Morphine. The broncho-constrictor action of morphine and its derivatives has been emphasized especially by Jackson. His experiments were performed chiefly on dogs. In experiments on rabbits and cats, I have found that doses corresponding to ten times the therapeutic dose per kilogram used in man produce only a slight broncho-constriction. Unless the quantitative reaction in man differs widely from that in those animals, the effect of therapeutic doses of morphine on the bronchioles is too slight to contra-indicate the use of morphine (in gas-poisoning for example), should it be found for other reasons necessary to employ it.

Broncho-dilators. Though, in the acute stage of chlorine poisoning, broncho dilators seemed to be of no practical utility, it was thought likely that other poisonous gases might produce more distinct and lasting broncho-constriction, for the relief of which broncho-dilators would be valuable. Of the three most commonly used broncho-dilators—atropin, adrenalin, and nitrites—*atropin* in sufficient doses seemed to be most efficacious in removing a broncho-constriction produced reflexly or by stimulation of the vagus nerve in any part of its course. If the bronchial secretion is considerably increased coincidently with the bronchial constriction, as for example by pilocarpine, atropin usually does not completely remove the obstruction to the entry of air into the lung. This is probably due not to its failure to dilate the bronchi but to its diminishing the bronchial secretion, rendering it more viscid and thus blocking the air-way. On the other hand, *adrenalin*, which dilates the bronchi by stimulating the sympathetic nerve-ends instead of, like atropin, by paralysing the vagus terminals, has no marked effect on the bronchial secretion, and is thus safer for general use. One point in regard to the action of adrenalin on the bronchi may be mentioned. It is generally stated that adrenalin dilates the bronchi only when they are previously constricted by, e.g., pilocarpine. This statement is too absolute. In the decerebrate cat, if sufficient time is allowed for elimination of the anaesthetic, adrenalin produces a slight but definite dilation of the bronchi, even in the absence of any artificial constriction. This result is more credible because otherwise it would mean that the bronchi are normally in a condition of maximum dilation, and, if so, lose the benefit of their double nerve supply under ordinary conditions. The mechanism would certainly be more flexible if the calibre of the bronchi was normally an intermediate one, capable of either increase or diminution as the result of sympathetic or vagus activity respectively.

This apparently is not the case, though, so far as can be judged from such experiments, the normal calibre seems to be somewhere near that of maximum dilatation. In my experiments nitrites (inhalation of amyl nitrite or intravenous injection of sodium nitrite) produced a relatively slight dilatation of the bronchi even in doses which caused a profound fall of blood-pressure. For practical purposes they appear to be much less valuable than either atropin or adrenalin.

Urethane. Considering the remarkable effect that urethane, when used as a general anaesthetic, exerts in preventing the occurrence of broncho-constriction which would normally be produced by ergamine, arecolin, &c., it was thought possible that intravenous injection of smaller doses of urethane might be able to dilate the bronchi when previously constricted by those drugs, in which case it might have proved of clinical value as a broncho-dilator. Experimentally this was not found to be the case; at least it certainly has no immediate effect in dilating the bronchi previously constricted. When urethane is used as an anaesthetic it is usually allowed at least half an hour to develop its anaesthetic effects before the animal is used for experiment. The probability is that its action on the bronchi—which is not yet sufficiently explained—takes a considerable time to develop. It does not appear, therefore, to possess any practical value for producing an immediate dilatation of the bronchi.

DESCRIPTION OF TRACINGS.

PLATE 2, FIG. 1. Rabbit under chloroform-ether anaesthesia. Funnel-tambour record of lung expansion with artificial respiration. Showing diminution of lung expansion (constriction of bronchi) by ergamine.

PLATE 3, FIG. 2. Rabbit under deep urethane anaesthesia. Conditions of experiment otherwise the same as in Fig. 1. Showing absence of effect of ergamine on bronchi.

FIG. 3. Cat decerebrate. Funnel-tambour record of lung expansion with artificial respiration. Showing transient reflex constriction of bronchi by inhalation of chlorine, 1 in 2,000.

FIG. 4. Rabbit under ether anaesthesia; natural respiration.
R. = Stethograph record of respiration, upstroke = inspiration.
I.P. = intrapleural pressure, downstroke = negative pressure = inspiration.
B.P. = blood-pressure.
Showing constriction of bronchi, acceleration of respiration, and fall of blood-pressure by inhalation of chlorine, 1 in 2,000.

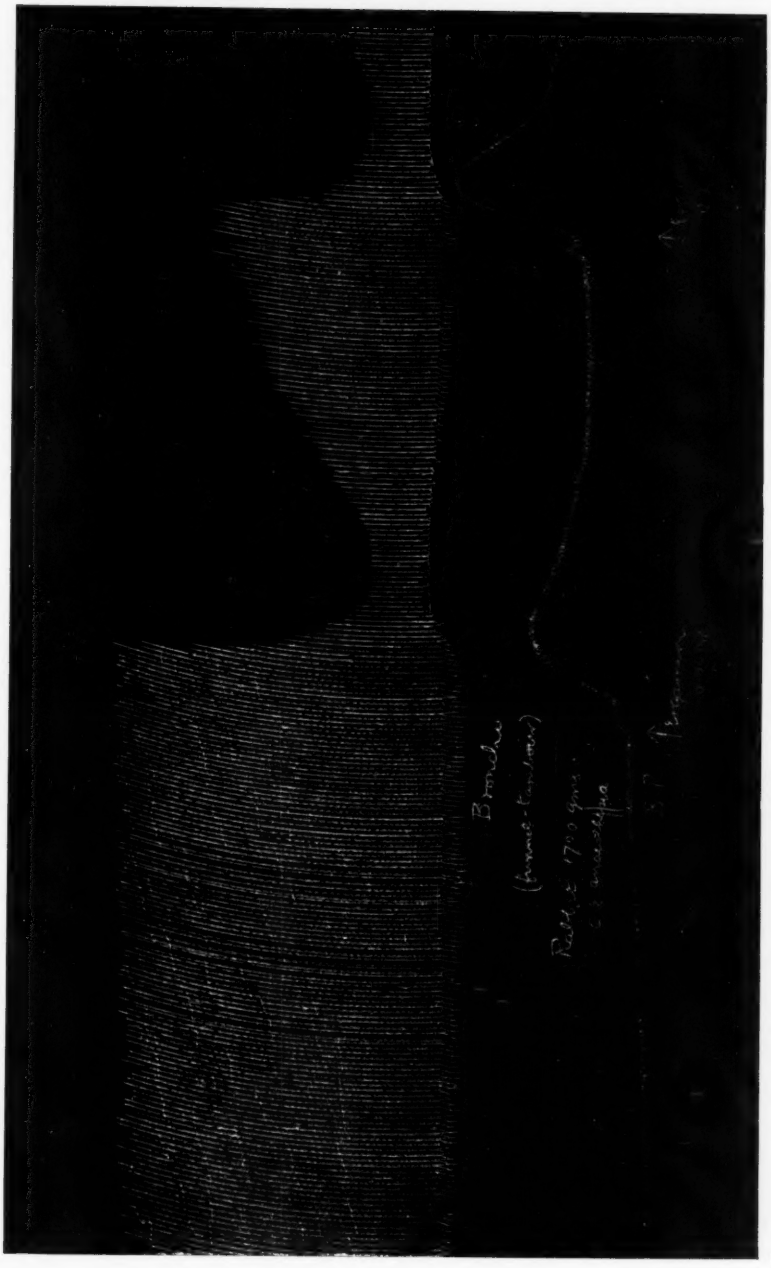

FIG. 1.

Qu

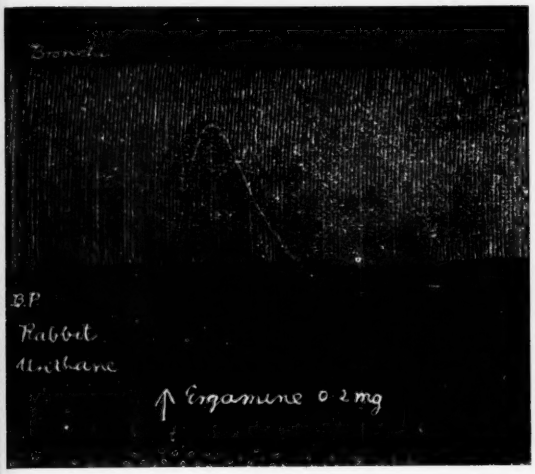

FIG. 2

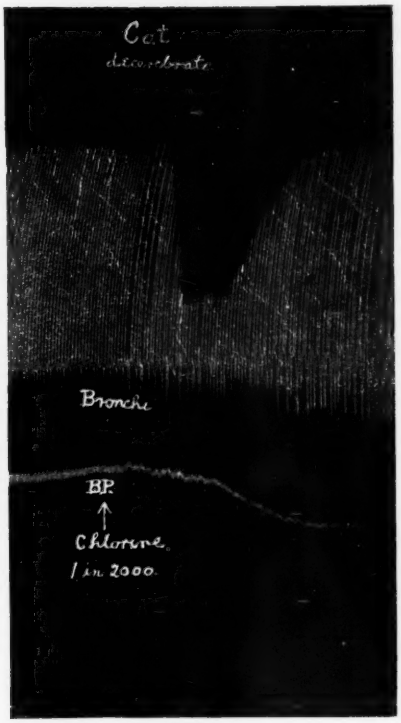

FIG. 3.

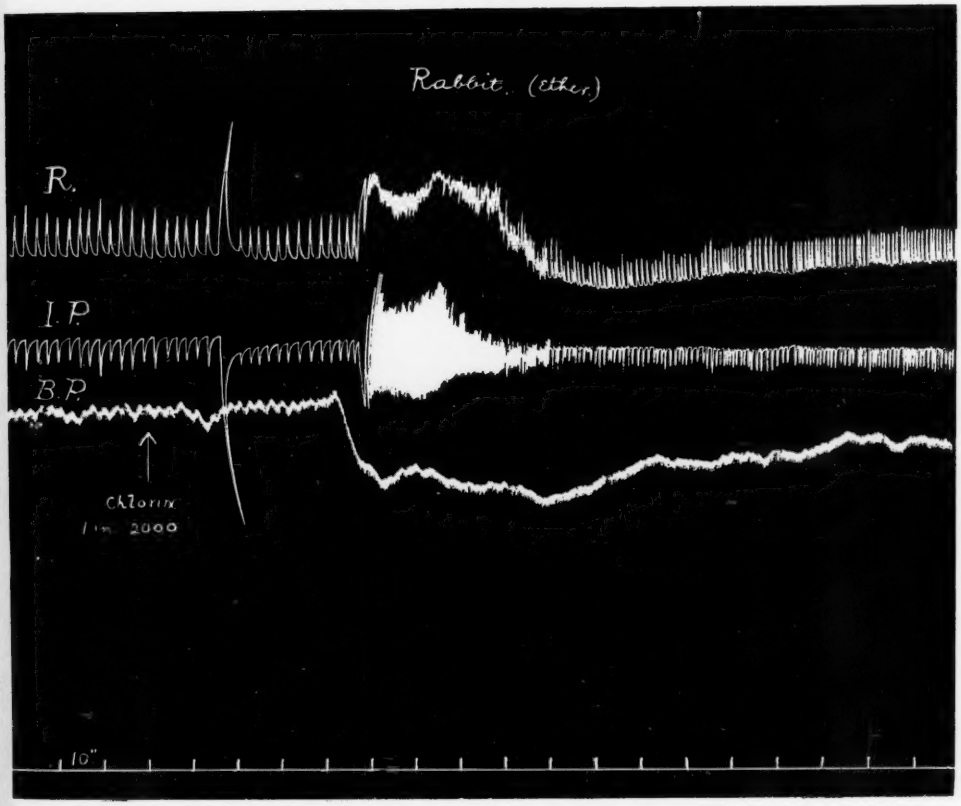

FIG. 4.

THE EFFECTS OF MULTIPLE EMBOLISM OF PULMONARY ARTERIOLES

By JOHN SHAW DUNN

(From the Physiological Department, R.E. Experimental Station, Porton)

Among the pathological phenomena which result from inhalation of pulmonary irritant gases it may readily be observed that the capillary blood-vessels in the lungs exhibit evidence of injury at very early stages and throughout large areas of tissue (1). The damaged capillaries soon become thrombosed and therefore impermeable to the blood-stream, and by so much the bed of the pulmonary circulation is restricted. It has seemed important to know to what extent the actual blockage of vessels may contribute to the inefficiency of the circulatory and respiratory functions which soon follows, but in gas-poisoning the vascular blockage is too much complicated by other deleterious factors to allow of any clear judgement being formulated on this point. The intention of the present research was to produce a similar obstruction of minute pulmonary vessels by simple mechanical means and observe the effects on the circulation and respiration. The facts which have been obtained possess a certain amount of value in this direction, although it has not been found possible to produce a condition of uncomplicated vascular obstruction for any great length of time. Nevertheless many features have been observed which are of interest in relation to the physiology of respiration and to alterations which occur in disease.

Methods.

The animals used were chiefly goats: observations were also made on a few dogs, cats, and rabbits. The substance employed to produce embolism was an emulsion of freshly prepared potato starch. Potatoes were scraped down on a grater and the débris was shaken up in a large bulk of physiological saline solution and filtered through loose gauze. The starch granules were of high specific gravity, and an almost pure sediment could be obtained very quickly by one or two washings and sedimentations. The purified sediment was finally allowed to deposit in a graduated cylinder, measured, and then shaken up with three times the amount of saline. The suspension was used unsterilized, as the experiments never extended over more than a few hours. In describing the

experiments this 1 in 4 suspension is referred to as 'starch'. Doses were introduced into the jugular vein or into the right ventricle from a syringe fitted with a hollow needle of about 0·75 mm. bore.

In a few experiments oil was employed to produce embolism, but, as is well known, oil can pass to some extent through the pulmonary capillaries and reach the systemic circulation, thus rendering possible the development of lesions in the brain and other organs. Starch appeared to be quite free from this objection, for in animals dosed with it no granules were ever observed in the cerebral or renal vessels, though these were examined repeatedly.

For certain experiments a general anaesthetic was necessary. Chloroform was found unsuitable, the dosage being difficult to regulate, and the respiratory rate being apt to vary from the effect of the anaesthetic alone.

Urethane, in a dose of 1 grm. per kilo, was found to give satisfactory results, and did not modify the usual symptoms of embolism. The anaesthetized animals tended to die more quickly than the unanaesthetized, but this did not interfere seriously with the experiments in question.

Immediate Effects of Embolism.

The result of introducing a dose of starch into a vein varied greatly according to the amount injected. The effects of relatively large doses will be described first.

I. *Large doses.*

From 40 to 75 c.c. of starch administered to four goats of 16 to 19 kilos caused death in from five to thirty minutes. The injections gave rise to acceleration of the respiratory rate such as will be more fully described later. In these animals attention was directed mainly to changes in the venous blood-pressure, and in two to the arterial blood-pressure. The venous pressure was measured by a U-manometer filled with 10 per cent. sodium citrate: this was connected with rubber pressure tubing to a hollow needle, both being filled with the citrate, and the needle was thrust into the jugular vein. The pressures which were observed on this manometer are stated in terms of millimetres of mercury. The systemic arterial pressure was measured from the carotid by a mercury manometer recording on a moving drum. The results of the four experiments are shown in tabular form:

TABLE I.

Goat No.	Weight in kilos.	Amount of Starch.	*Venous Pressure.* Normal.	*Venous Pressure.* Maximum after Emb.	*Arterial Pressure.* Normal.	*Arterial Pressure.* 3 minutes after Emb.
		c.c.	mm. Hg.	mm. Hg.	mm. Hg.	mm. Hg.
D 89	16·4	40	3·0	17·2	—	—
D 90	19·1	75	3·1	25·8	—	—
D 93	17·0	60	2·8	22·8	118	35
D 94	17·7	60	3·1	20·0	110	26

In these four goats death occurred at the following intervals after injection of the starch: D 89, 23 min.; D 90, 30 min.; D 93, 5 min.; D 94, 5 min. In each case the venous pressure rose rapidly, reaching a maximum very shortly before death. The pressure in the veins had approximated to that in the arteries by that time. Fig. 1 is a reproduction of the tracing obtained in D 93, and illustrates the time incidence of the various changes and the alteration in respiratory rate. In all of these animals the respirations came to a standstill one or two minutes before the heart ceased to beat.

On post-mortem examination the lungs of these goats exhibited some minute haemorrhages scattered on their surfaces and also in their substance. Apart from this the lungs appeared normal and underwent the normal degree of collapse when the thorax was opened. On histological examination all pulmonary arterioles up to a diameter of 1·5 or 2·0 mm. were filled with starch granules and appeared completely blocked.

The fall in systemic blood-pressure and rise in venous pressure in these animals developed very rapidly after injection of the emboli, and it may be that the pressure alterations were due purely to damming up of blood in the venous system as a result of obstruction of pulmonary vessels: the histological picture would suggest that this explanation is correct. It is of interest to note that failure of the respiratory centre, which no doubt depended on insufficient blood-supply, occurred in all cases one or two minutes before the heart ceased to beat, although the blood-supply to the cardiac muscle must have been similarly deficient.

II. *Moderate doses.*

The administration of smaller doses of starch, insufficient to cause sudden death, was followed by acute illness with characteristic symptoms, and death ensued in 1¼ to 8 hours, with peculiar pulmonary lesions. The dose of starch most frequently employed was 15 c.c. for goats of 20

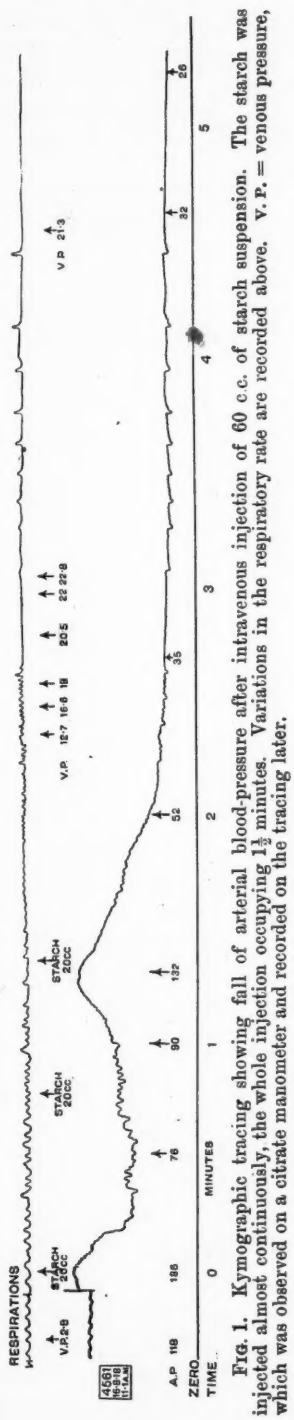

FIG. 1. Kymographic tracing showing fall of arterial blood-pressure after intravenous injection of 60 c.c. of starch suspension. The starch was injected almost continuously, the whole injection occupying 1½ minutes. Variations in the respiratory rate are recorded above. V. P. = venous pressure, which was observed on a citrate manometer and recorded on the tracing later.

to 30 kilos, but even 5 c.c. of the suspension, or 5 c.c. of oil, brought about very similar results.

The most striking alteration observed during life in these animals was in the rate and character of the respirations. Immediately after the injection there followed a period of complete or partial inhibition of respiration, lasting from

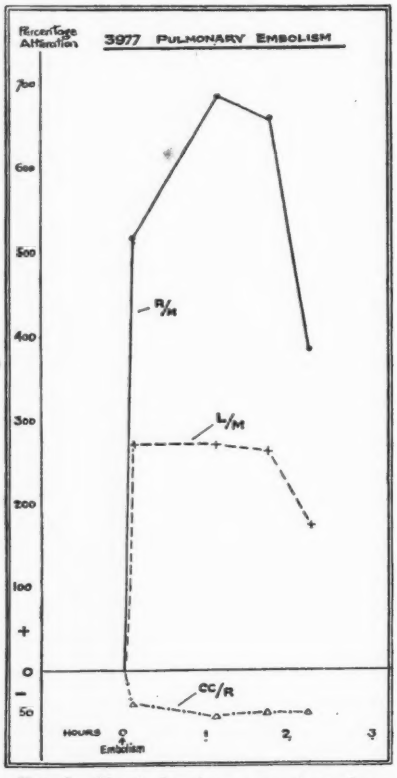

FIG. 2. Chart showing percentage alterations in rate of respiration (R/M), total ventilation of lungs (L/M), and depth of each respiration (CC/R), throughout the course of an embolism experiment. The zero line represents the normal for each factor and variations in each are recorded in terms of the normal, so as to make all mutually comparable. As the percentage rise in rate exceeds the percentage rise in ventilation the depth of respiration falls below the normal.

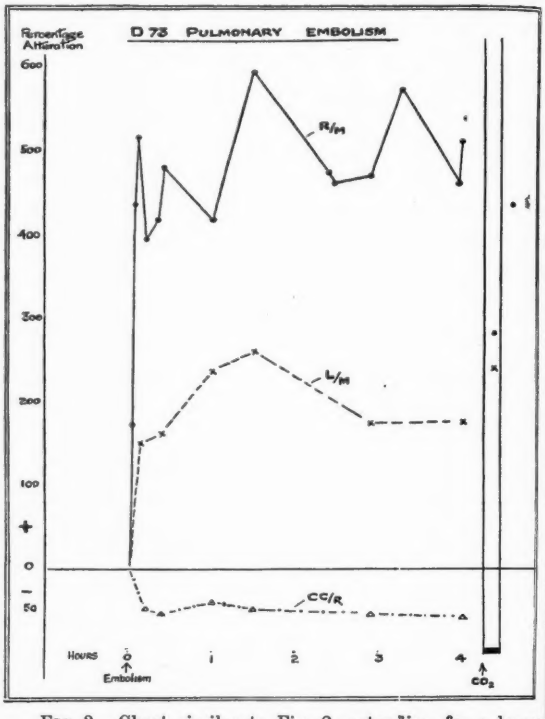

FIG. 3. Chart similar to Fig. 2, extending for a longer time. The effect of breathing CO_2 is shown at the end, where rate was diminished and depth restored to normal. These changes were only temporary, and the original condition returned when CO_2 was stopped.

one to seven minutes. The rate then began to quicken and almost at once rose to three, seven, nine, or even fourteen times the normal. The acceleration of rate might reach a maximum at once and continue high with slight fluctuations till death, or might attain a maximum at some intermediate period. In any case it never returned to near the normal figure. In addition to being rapid the respiration was shallower than normal, though the total amount of air breathed

per minute was almost always increased. Eight typical examples, which were fully investigated, are shown in Table II. Figs. 2 and 3 are charts which illustrate the percentage alterations in rate, amount of air breathed, and depth of respiration in two animals throughout the course of the experiments.

TABLE II.

Table showing Alterations in Respiration after Embolism.

Goat No.	Dose of Starch in c.c.	*Respiration Rate.* Normal.	*Respiration Rate.* Maximum after Embolism.	*Litres of Air breathed per minute.* Normal.	*Litres of Air breathed per minute.* After Embolism.	*Amount of Air per Respiration in c.c.* Normal.	*Amount of Air per Respiration in c.c.* After Embolism.
D 42	5	22	200	7·35	17·25	380	90
D 50	30	17	79	8·4	22·4	495	283
D 52	20	13	46	4·0	8·8	310	192
D 68	15	20	160	6·0	22·0	290	136
D 69	20	15	55	4·2	4·3	280	78
D 73	15	14	99	4·9	16·6	350	167
D 76	15	12	89	5·4	16·2	448	182
D 77	13	13	60	4·5	6·4	333	107

The rapid shallow respiration thus produced by a direct attack on the blood-vessels of the lungs was very similar to that which results from inhalation of pulmonary irritants, and an animal with embolism might easily have been mistaken for a gassed animal. As a rule the pulse-rate was not much affected at first, but it gradually quickened, frequently reaching 140 to 160 per minute before death. In the later stages of experiments oedema fluid poured from the mouth in some animals, but this symptom was not always noted.

Several series of experiments were carried out to determine, if possible, the mechanism of production of the dyspnoea. These observations were directed to:

(1) The oxygen saturation of arterial and venous blood.

(2) The rate of the circulation in embolized animals.

(3) The effects on systemic and venous blood-pressures.

(4) The part played by carbon dioxide.

(5) The influence of the vagus nerve.

(1) In embolized goats in which the condition of dyspnoea was fully established, samples of blood were withdrawn without an anaesthetic by needle-puncture from the right and left ventricles of the heart, and the percentage saturation of oxygen in the samples was measured by means of the Barcroft differential manometer. The results of two experiments are given below:

	Percentage Saturations of Oxygen.			
	Arterial.	Venous.	Respiration Rate per min.	Depth of each Respiration.
				c.c.
(A) Goat D 42: Weight 24·1 kilos. Dose 5 c.c. starch.				
Normal	95	64	22	380
After embolism—				
6½ minutes	99	61	200	90
1 hr. 17 min.	96	62	50	207
(B) Goat D 50: Weight 38·6 kilos. Dose 30 c.c. starch.				
Normal	96	58	17	496
After embolism—				
3 hrs. 30 min.	94	—	79	283

From these figures it is quite clear that the dyspnoea was not due to, nor did it necessarily give rise to, desaturation of oxygen in the arterial or venous blood. This result was to be expected, as the experimental procedure did not primarily interfere in any way with the access of air to the alveoli: and any blood which could pass through the lung capillaries had ample access to air, at any rate in the earlier hours of experiment. It was found, however, that towards the end of an experiment some desaturation might occur. This might be due to late development of pulmonary oedema, to the ventilation of the lungs becoming inadequate from failure of the respiratory centre, or to spasm of the bronchioles, such as will be described later.

(2) *The rate of the circulation.* The method by which this was measured is fully described in another communication (2), and only a brief outline will be given here. At the time that blood samples were withdrawn from the right and left ventricles of the heart, the expired air of the animals was collected in a Douglas bag for a known time. The air sample was measured and analysed as regards its content of oxygen and carbon dioxide. By comparison with the composition of atmospheric air it could then be ascertained how much oxygen the animal was consuming per minute. From the blood samples taken at the same time could be ascertained the difference between the amount of oxygen in a cubic centimetre of arterial and in a cubic centimetre of venous blood: that is to say, it could be determined how much oxygen was taken up by each cubic centimetre of blood in passing through the lung. By dividing the former figure by the latter a measure was obtained of the amount of blood which passed through the lungs in one minute, and therefore of the rate of the circulation.

Numerous estimates of the circulation rate have been carried out with apparent success on the above lines, and on normal resting animals the results are fairly concordant. In animals suffering from embolism the procedure of puncturing the heart was less easy to perform successfully, on account of the rapid respiratory movements, in which the heart was involved. The figures obtained in five embolism experiments are shown below:

TABLE III.

Measurements of Rate of Circulation in Embolism.

	Respiration Rate.	Volume of Blood passing through Lungs per minute.
		c.c.
Goat D 49:		
Weight 31·4 kilos.		
Dose 35 c.c. starch.		
Normal 1st Est.	15	3820
Normal 2nd Est.	14	2920
1 hour after embolism	68	2100
Goat D 50:		
Weight 38·6 kilos.		
Dose 30 c.c. starch.		
Normal	12	5600
2½ hours after embolism	66	4120
Goat D 52:		
Weight 27·7 kilos.		
Dose 20 c.c. starch.		
Normal	12	2880
35 minutes after embolism	46	4760
Goat D 116:		
Weight 28·6 kilos.		
Dose 15 c.c. starch.		
Normal 1st Est.	19·3	1370
Normal 2nd Est.	22·5	1510
Normal 3rd Est.	22	1900
After embolism—		
50 minutes	35	1950
70 minutes	29	1550
Goat D 115:		
Weight 23·6 kilos.		
Dose 11 c.c. starch.		
Normal	25	2350
After embolism—		
11 minutes	57·5	930
1½ hours	41	2910

The results of these experiments show no constant relationship between the dyspnoea and alterations in the circulation rate. In the first and second, where dyspnoea was most severe, there was a fall; in the third, with rather less severe dyspnoea, there was a considerable rise in the circulation rate. In the fourth, with less severe dyspnoea, the rate was unchanged after embolism. In the fifth there was a very considerable fall immediately after embolism, when dyspnoea was worst, which passed off, and a measurement taken 1½ hours after the embolism showed that the normal rate had been re-established, though the dyspnoea was still fairly severe. On the whole it would appear that the dyspnoea is not determined by a lowered rate of the circulation, but that embolism can produce a diminution of the blood-flow, especially at first. It is evident that examinations would have to be made more frequently in each animal, especially at early periods after embolism, in order to obtain a complete account of the alterations in each case, but in embolized goats there is considerable difficulty in making successful punctures, and most difficulty has been encountered in the earlier stages after injection, as a result of struggling.

(3) *Arterial and venous blood-pressure.* In two experiments the arterial pressure was measured before and after embolism, by kymograph. Urethane was employed as anaesthetic.

	Respiration Rate.	Arterial Pressure.
Goat D 56:		
Weight 27 kilos.		
Dose 15 c.c. starch.		mm. Hg.
Normal	12	116–120
After embolism—		
9 minutes	52	126
19 minutes	66	136
44 minutes	46	115
1 hr. 4 min.	46	95
1 hr. 17 min.	44	68
Goat D 61:		
Weight 22·1 kilos.		
Dose 15 c.c. starch.		
Normal	Not recorded	134
After embolism—		
6 minutes	Raised	128
10 minutes	,,	134
38 minutes	,,	130
53 minutes	,,	96
1 hr. 23 min.	,,	72

Fig. 4 is the tracing obtained in the case of D 56. In this animal the blood-pressure was actually raised for a short period after embolism. These experiments show maintenance of arterial pressure at or near the normal level for about an hour after injection of the emboli, during which time the dyspnoea was continuously severe. The onset and maintenance of the rapid respiratory rate is clearly not due to fall in arterial pressure.

The blood-pressure in the great veins was measured in six goats at various periods, before and after embolism. The measurements were made with the citrate manometer employed for the same purpose where larger doses of starch had been administered. No anaesthetics were used.

The results are shown below:

	Respiration Rate.	Venous Blood-pressure.
Goat D 68:		
Weight 20 kilos.		
Dose 15 c.c. starch.		mm. Hg.
Normal	20	6·0
After embolism—		
15 minutes	127	3·3
1 hr. 16 min.	156	2·0
2 hours	99	4·5
Goat D 69:		
Weight 23·2 kilos.		
Dose 15 c.c. starch.		
Normal	14	2·0
After embolism—		
1 hr. 50 min.	55	1·1
Goat D 73:		
Weight 30 kilos.		
Dose 15 c.c. starch.		
Normal	16	3·5
After embolism—		
30 minutes	80	2·6
3 hrs. 24 min.	96	3·8

	Respiration Rate.	Venous Blood-pressure.
Goat D 77:		
Weight 24·1 kilos.		
Dose 13 c.c. starch.		mm. Hg.
Normal	13	3·5
After embolism—		
3 hrs. 15 min.	57	2·3
Goat D 115:		
Weight 23·6 kilos.		
Dose 11 c.c. starch.		
Normal	25	3·5
After embolism—		
7 minutes	57·5	12·0
26 minutes	44	10·0
1½ hours	41	3·0
Goat D 116:		
Weight 28·6 kilos.		
Dose 15 c.c. starch.		
Normal	22	6·0
After embolism—		
13 minutes	48	11·0
1 hour	35	5·0

In the first four experiments there was no conspicuous change in the venous pressure after embolism, while in each case the dyspnoea was well marked, and in the first it was of extreme severity. In the fifth and sixth a definite rise took place immediately after the injection, but this subsided later while the dyspnoea continued. It is thus clear that the dyspnoea can arise and continue in absence of any alteration in the venous pressure.

In a few animals the immediate and late alterations in the blood-pressure in the right ventricle were measured, the results being complementary to the above. The procedure was carried out in experiments where cardiac punctures were performed for the purpose of collecting blood-samples. After the samples had been taken the hollow needle in the right ventricle was attached by pressure tubing to a Hurthle manometer. The rubber tubing and the tambour of the manometer were filled with a continuous column of 10 per cent. sodium citrate. The pressure variations in the ventricular cavity could thus be recorded on a drum from the tambour lever. After a tracing was taken in this way the needle was withdrawn and detached from the rubber tube. By raising or lowering the end of the tube, still full of citrate, a scale was obtained showing the heights on the tracing corresponding to known columns of citrate. These pressures were then converted to millimetres of mercury.

Fig. 5 is the tracing obtained in one experiment where 2 c.c. and later 3 c.c. of oil were injected into the right ventricle. The first injection caused a slight increase in diastolic pressure only. The second injection, following immediately, caused a considerable rise in both systolic and diastolic pressures:

	Average Diastolic Pressure.	Average Systolic Pressure.
	mm. Hg.	mm. Hg.
Before injection	5·5	18·0
After 1st injection	6·5	18 0
After 2nd injection	14·0	23·0
10 minutes later	4·0	17·0

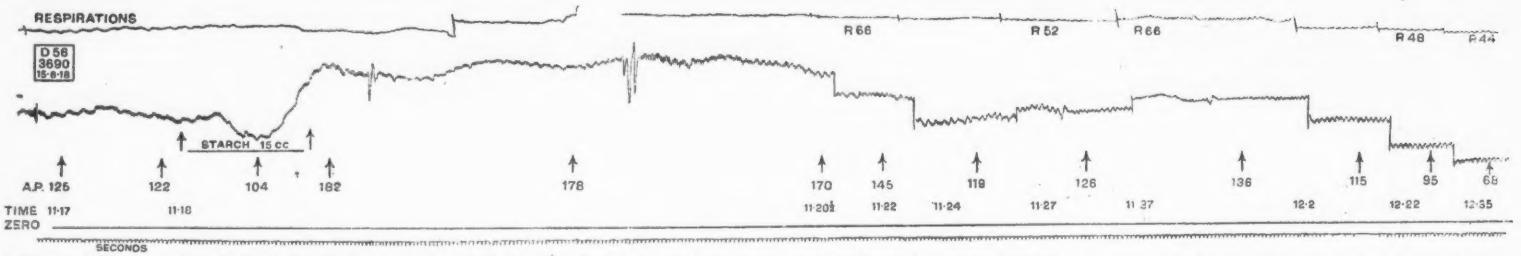

FIG. 4. Kymographic tracing showing range of arterial pressure for 1 hr. 18 min. after injection of 15 c.c. of starch. A record of the respiratory rate is given above.

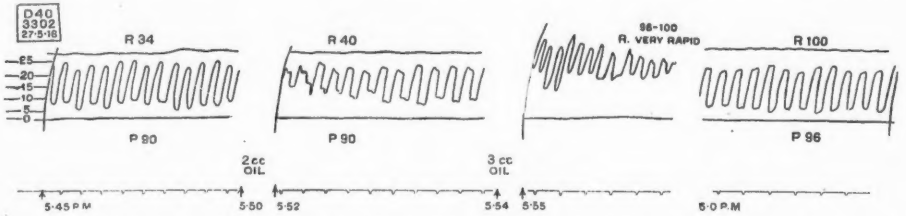

FIG. 5. Tracing taken by Hurthle's manometer of pressure variations in cavity of right ventricle immediately after injections of oil. After the second injection, 3 c.c. of oil, there is a well-marked but transient rise both in systolic and diastolic pressures. Five minutes later both have returned to normal.

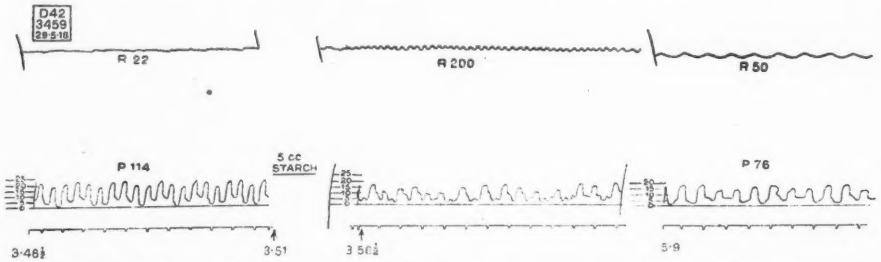

FIG. 6. Tracing similar to Fig. 5, from another experiment. No rise in pressure is recorded 10 minutes after injection. Note great rise of respiration rate, recorded above.

This effect was quite transient, as is shown by the part of the tracing taken ten minutes after the second injection, when the pressures were almost the same as before experiment.

A similar experiment in which 5 c.c. of starch were injected showed no rise in the right ventricular pressures after embolism (Fig. 6).

The former experiment shows that there may be a transient damming up of blood in the right heart even after a small dose of emboli, but evidently this can be very rapidly accommodated. The observations on venous pressures at later periods stated above also show how complete the compensation of the circulation may be made.

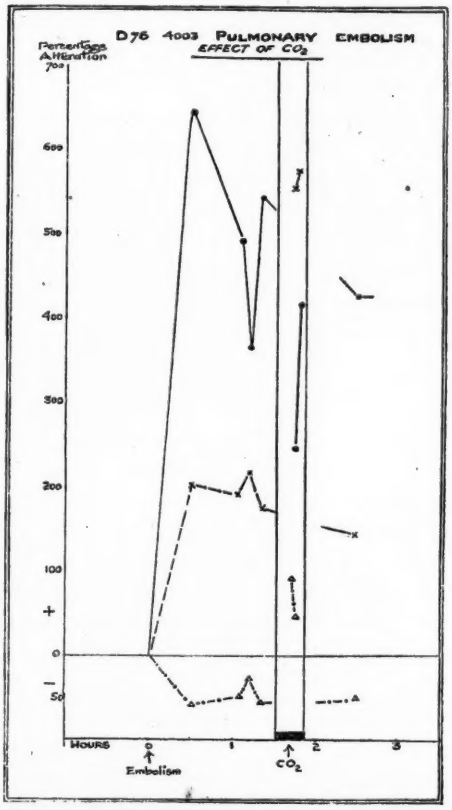

FIG. 7. Chart similar to Figs. 2 and 3, showing first the usual effects of embolism. CO_2 was administered 1 hr. 33 min. after the start of the experiment and produced fall in rate, great increase in ventilation, and increase in depth to above normal. After CO_2 was taken off the old rates were re-established.

(4) A possibility which received consideration was that the limitation of the pulmonary circulation by embolism might so diminish the vascular area available for exchange of carbon dioxide that the pressure of this gas in the blood would rise and thus cause dyspnoea. Against this it is to be noted that

the type of dyspnoea produced by embolism differed markedly from that due to inhalation of carbon dioxide. Normal goats which were made to breathe excess of carbon dioxide were found to exhibit the usual type of dyspnoea—a moderate rise of rate, a marked increase in volume breathed, and a very marked increase in depth of each respiration. Another point against the chemical factor being concerned was that the degree of dyspnoea caused by embolism was not proportional to the amount of embolic material injected, but could be quite severe after a small dose. Some experiments were performed to test this point further.

Two goats which already had dyspnoea from embolism were made to breathe excess carbon dioxide by the following means: A tightly-fitting mask was applied over the face of the animal and a rubber tube of 1-inch bore and two yards long was attached to the main outlet of the mask. At the free end of the tube a Y-piece was attached, one limb of which carried an inspiratory and the other an expiratory valve. From the latter the amount of air corresponding to the expired air could be collected in a Douglas bag for measurement. The effect of the long tube was to increase the animal's 'dead space', and thus cause it to re-breathe its own carbon dioxide. The mask was fitted with two additional apertures which could be closed at will: through one of these additional oxygen could be given as required from a cylinder: from the other, samples of the atmosphere that the animal was breathing could be collected for analysis. The results of two experiments were as follows (see also Figs. 3 and 7):

	Respiration Rate per min.	Total Ventilation (litres per min.).	Depth of each Respiration in c.c.
Goat D 73: Weight 30 kilos. Dose 15 c.c. starch.			
Normal	14	4	350
After embolism—			
4 hours	88	12·1	138
4½ hours (Breathing excess CO_2)	55	21·1	382
Goat D 76: Weight 30·4 kilos. Dose 15 c.c. starch.			
Normal	12	5·4	448
After embolism—			
1½ hours	77	14·8	192
1¾ hours (Breathing excess CO_2)	41	35·1	846

These two experiments show that when the shallow type of breathing had been fully established the breathing of carbon dioxide very soon produced increase in depth of the respirations and in the total ventilation. In one instance the depth of each respiration was restored to the normal range; in the other the normal was almost doubled. The animals were thus quite sensitive to a rise of carbon dioxide in the alveolar air.

In three experiments the total CO_2 content of the arterial blood was estimated before and after embolism. The estimation was carried out in the Barcroft differential manometer, using tartaric acid to expel the gas. The following results were obtained:

Goat.	Respiration Rate per minute.	Arterial CO_2 (volumes %).
D 52. Normal	12	64
After embolism, 30 minutes	46	67
D 49. Normal	14	57
After embolism, 1 hour	68	50
D 50. Normal	12	60
After embolism, 2½ hours	66	57

In the first experiment a slight increase is noted: in the second and third a decrease. So far as the figures go they show no certain diminution of the fixed alkalinity of the blood. Taken along with the previous set of experiments, which showed a normal response to the breathing of carbon dioxide in embolized animals, they indicate that the dyspnoea is not produced by any considerable change in the carbon dioxide of the blood. In view of the great increase in respiratory rate a fall in the carbon dioxide of the blood might have been expected, but apparently this did not take place. This may be because, though a large quantity of air was passing in and out of the lung, only a proportion of it came in contact with blood-vessels in which the circulation was normal, so that only that proportion was able to take up carbon dioxide from the blood in normal fashion.

(5) *The influence of the vagus nerve.* On the whole it was considered most probable that the dyspnoea was brought about by reflex action, initiated by stimulation of sensory nerve-endings in the lungs. A fact which favoured this view was that the dyspnoea was characterized mainly by an alteration in rate of respiration. The following experiments show the influence of section of the vagus nerves.

(*a*) In two goats both vagi were divided in the neck under urethane. Subsequently both animals received intravenous injections of 15 c.c. of starch. In each case the respiration rate, which after section of the nerves was in one case 14 and in the other 16 per minute, remained quite unaltered for three-quarters of an hour, at which time the animals were killed. In other animals in which the vagi were divided and no emboli injected the rates have been no slower.

(*b*) Goat D 73 received an injection of 15 c.c. of starch. The rate of respiration rose from the normal of 14 to 88 per minute in six minutes. Four and a half hours later the rate was 55. At that time both vagi were divided, and the rate fell at once to 15 per minute. It continued at this slow rate for half an hour, at which time the animal was killed.

(*c*) In three goats the left vagus nerve only was divided in the neck. A dose of 15 c.c. of starch administered subsequently produced in each case the typical reaction of rapid and shallow respiration.

From the evidence of these experiments there seems to be no doubt that the dyspnoea of embolism is occasioned by impulses which pass through the vagi. It is perhaps of special importance to note that the shock caused by

cutting one of the nerves did not interfere with the usual respiratory reaction so long as the other nerve was intact.

Concentration of the Blood after Embolism.

In the course of eight experiments with embolism the haemoglobin value was estimated and compared with the normal. In five of the animals there was a rise in the percentage of haemoglobin, indicating some degree of concentration of the blood. The amount of the probable loss of serum from the blood which this concentration indicated was calculated on the basis that the original blood-volume would be 5·5 per cent. of the body weight. In the following table these figures are stated and compared with the calculated amount of abnormal fluid in the lungs as shown by post-mortem examination. In each case the final estimation of the haemoglobin was made just before the death of the animal.

Goat.	Respiration Rate.	Percentage Alteration in Haemo-globin.	Calculated Loss of Fluid from Blood in c.c.	Time of Death after Embolism.	Calculated Extra Fluid in Lungs.
(1) D 54 (*a*)	140	+15·5	214	Died 1¼ hrs.	530
(2) D 54 (*b*)	104	+ 8·5	106	Died 3 hrs.	370
(3) D 54 (*c*)	94	+17	250	Died 2¼ hrs.	550
(4) D 54 (*d*)	62	+ 8·1	116	Killed 8 hrs.	170
(5) D 54 (*e*)	66	+ 4	64	Killed 7 hrs.	210
(6) D 54 (*f*)	52	0	0	Killed 7½ hrs.	0
(7) D 73	87	0	0	Killed 4⅝ hrs.	330
(8) D 49	68	+28	500	Killed 1 hr.	190

In three cases (5, 6, and 7) there was no evidence of concentration of the blood, though two of the animals showed some oedema of the lungs. In the remaining five it occurred to some extent, but was in no case very severe. Three of these animals died. In these three and in the fourth, which was killed at eight hours, there was sufficient escape of oedema fluid into the lungs to account for the loss of serum from the blood. In the other animal (8), which showed the greatest concentration of all, there was very little pulmonary oedema.

These data show no certain relationship between pulmonary oedema and concentration of the blood.

Pathological Examination.

In animals which were killed within an hour of injection of the emboli, as in those which died in a less time from large doses, the only visible change in the lungs was the presence of scattered petechial haemorrhages under the pleurae and in the substance of the organs. In those which died or were killed at later periods the lungs presented important alterations. The organs showed great diminution or absence of the normal collapse on opening of the thorax. This condition of permanent distension was most marked in animals which died of embolism, and in these the lungs usually retained the full size and shape of

the thoracic cavity. There was no gross obstruction in the tracheae or bronchi to account for this phenomenon, and an explanation was only obtained by microscopic examination, as will be shown. Apart from the distension, the lungs showed, on naked-eye examination, a considerable amount of oedema in the interstitial planes and under the pleurae. The interlobular planes were opened up and appeared as wide fissures full of clear fluid. Fluid amounting to 100 or 150 c.c. was found in the pleural cavities in some instances. Where death occurred after about five hours there was also some evidence of alveolar oedema. In one case this was so abundant as to render the lungs indistinguishable from those of an animal which had died after gassing with a pulmonary irritant. The oedema, whether interstitial or alveolar, greatly increased the weight of the lungs, and therefore the lung : heart ratio. In severe examples this ratio rose to 6·0/1, from the normal average of 2·4/1. In gassed lungs this would certainly represent a severe degree of casualty. In the fatal cases there was also a great development of petechial haemorrhage, so that the pleural surfaces appeared haemorrhagic all over.

Histological examination. The starch granules were easily observed, impacted usually in the minute arterioles which radiate from around the bronchiolar terminations. The granules mostly occurred singly, where moderate doses of starch had been administered. Only a few granules were seen in alveolar walls, apparently in capillaries, and these were never far from the centres of the lobules, and therefore from the arterioles.

In relation to the impacted granules occurred the small haemorrhages already noted. The capillaries in the neighbourhood of these were much engorged with blood and not infrequently contained thrombi. The areas of engorgement probably represented vascular territories from which the direct blood-supply had been cut off. As a result the capillaries had filled up from collateral (capillary) supplies, but the circulation in them remained stagnant, so that the vessel-walls deteriorated and haemorrhage and thrombosis followed.

The presence of oedema was indicated in the interstitial tissue of the lung by wide separation of the fibres in connective-tissue planes and around bronchi and blood-vessels. Alveolar oedema was only observed in cases where the experiment had lasted four or five hours, and even then it did not appear bulky.

The explanation of the general over-distension of the lungs was found in a condition affecting the involuntary musculature of the atria or bronchiolar terminations and the infundibula. These strands of muscle were thickened and contracted, and were thereby so closely approximated one to another as to constrict or even close the orifices which they surrounded. Thus the normally wide lumina of the atria were almost abolished, and the muscular bands outlining the cavities were drawn close together around the necks of the infundibula. In the infundibula the interalveolar partitions were drawn tightly inwards and their free central edges sometimes met, thus closing the openings of alveoli. The cavities of the alveoli were generally rather distended, in

evidence of the fact, which could be observed from naked-eye examination of the lungs, that the air in them was imprisoned even after death. To be fully appreciated this condition must be carefully compared with that found in the normally collapsed lung of a healthy animal freshly killed. There the muscular tissue in the same situations is lax and contorted, and the individual bundles are so slender that they may be distinguished only by close scrutiny. It was remarkable that the bronchioles themselves, so far as they formed continuous tubes, usually showed no evidence of constriction.

The histological picture which has been described left little doubt that there was marked spasm of the musculature, though it seemed remarkable that a condition of tonic contraction should be so perfectly preserved after death. The relation between the impaction of starch granules in the vessels and spasm of the pulmonary muscle is not certainly known, but it may be supposed that a reflex nervous mechanism connects the two. A reflex, initiated by the irritation of foreign bodies in the arterioles, might presumably summon a response either from ganglia in the pulmonary plexus or from the central nervous system by way of the vagus. Some experiments were done with the object of settling this point, but the results were inconclusive. In animals where both vagi had been cut either before or after injection of emboli no distension of the lungs or spasm of muscle was found. However, in these animals, death probably occurred sooner than it would have done had the nerves been intact, and the stage may not have been reached when spasm was to be looked for. In three animals in which one vagus only was divided the spastic condition developed as usual, and it affected both lungs equally in each case.

An almost identical anatomical condition has already been described (1) as occurring at times in the early stages of poisoning by pulmonary irritants. In these cases it is found within one or two hours of inhalation of gas, and sometimes, at any rate, within a very few minutes. It then precedes the appearance of pulmonary oedema. In the case of gassing the original stimulus is applied to the whole respiratory tract, including no doubt the pulmonary capillaries, but there is no reason to suppose that the injury of the latter is alone responsible for the reflex spasm.

The functional significance of the spasm, if it has any, is unknown. It might be suggested that it represents an attempt on the part of the body to regulate the ventilation of the lung and render it more effective. The closure of certain areas might be intended to cut off the air-supply from parts in which the pulmonary circulation was defective and direct it to those in which blood was circulating more normally. On the other hand, in fatal cases the condition is so universal, and so effectively imprisons the alveolar air, as to indicate that its general effect is deleterious and contributory to the fatal issue.

Discussion.

The methods adopted in this research are believed to provide, at first, an uncomplicated condition of multiple embolism of pulmonary arterioles. There is no reason to believe that any of the results which have been observed are due to lodgement of emboli in other organs than the lungs. In this respect these results may differ from those produced by experimental oil-embolism in animals, or from the phenomena of fat-embolism in the human subject. In the latter conditions a considerable amount of the embolic material passes through the pulmonary capillaries, and, entering the systemic circulation, may cause lesions in the brain and elsewhere.

Where a large dose of starch emboli causes sudden death it apparently acts in a very direct fashion. The arterial blood-pressure falls almost at once to a fatal level, and the pressure in the large veins rises simultaneously almost to the same figure, so that the circulation is brought to a standstill. It appears as if the passage of blood from the right to the left side of the heart were almost completely cut off in the lungs. There is also no doubt, from histological examination of the lungs in these animals, that the degree of obstruction of the pulmonary arterioles is very great.

Where the dose of starch is insufficient to cause sudden death, the blood-pressure in the right heart and great veins shows at most a transient rise immediately after the injection. Afterwards the venous pressure has been observed to remain at normal level for more than three hours in unanaesthetized goats, although during that time the animals showed symptoms of acute illness. The arterial blood-pressure, which has been recorded only in animals which were under the influence of a general anaesthetic, has remained at or above the normal level for an hour after similar doses. This maintenance of pressure during the first hour is of more significance than the subsequent fall, for there is no doubt that the anaesthetized animals die sooner after embolism than the unanaesthetized. From other experiments it would appear that there is no great permanent diminution in the amount of blood which passes through the lungs per minute with this order of dosage.

The maintenance of the arterial pressure and of the blood-flow in these experiments is all the more remarkable when it is considered that the vessels which are blocked are mainly arterioles and not capillaries. Whereas for any single occluded capillary the alternative routes are practically infinite, an arteriole is an end artery on a small scale, and represents a definite division of the main pulmonary artery, so that its whole function cannot be adequately taken over by any other vessel. In these facts we have definite evidence of a very considerable reserve of vascular area in the lungs. We know that a large number of pulmonary arterioles can be occluded and yet leave the circulation substantially maintained, at any rate for the resting animal. Therefore more blood must pass through the unobstructed arterioles than they are normally

called upon to accommodate. Theoretically this result might be attained in any one of three ways: (1) by diminution in the viscosity of the blood, (2) by increase of pressure in the pulmonary artery, and (3) by dilatation of the unobstructed vessels. It has been shown by estimation of the haemoglobin that there is no diminution of the concentration of the blood and therefore of viscosity, and direct measurement has shown no lasting rise of systolic pressure in the right ventricle, so we are driven to the third conclusion, that the pulmonary arterioles are dilated to provide compensation. In other words, we have indirect evidence that the amount of blood which passes through the pulmonary arterioles is subject to regulation apart from that which is obtained by alterations in the pressure of the blood in the pulmonary artery.

From the above considerations it would appear that the blockage of capillaries by thrombi in gas poisoning does not by itself constitute a serious obstruction to the circulation. In that condition, however, it is associated with other factors, such as pressure of alveolar fluid on the capillary walls, increase in the viscosity of the blood, and possible alterations in the texture of the endothelium in non-obstructed capillaries, and in the production of the total deleterious effect it may have a substantial share.

The peculiar form of dyspnoea caused by embolism is of special interest in that it appears to be determined by nervous influence. It follows almost immediately on introduction of the obstructive material, and the degree of its development may be quite disproportionate to the dose of emboli injected. The form of the dyspnoea is similar to that which rapidly follows inhalation of pulmonary irritants, and the two are in so far analogous that they are fully established before there is any production of oedema or other visible organic change in the lungs, and certainly long before there is any mechanical interference with the ventilation of the alveoli.

When death results from the less severe doses of emboli it is found that the primary obstruction of vessels has become complicated by secondary pathological changes in the lungs. These may also be observed in process of development in animals killed at intermediate periods. They comprise pulmonary oedema, mainly interstitial but in part alveolar, and spastic contraction of the atria and infundibula. The addition of these to the vascular blockage probably determines the late desaturation of oxygen in the arterial blood and ultimately the death of the animal.

The pulmonary spasm produced by embolism resembles in general that which is occasionally observed in gas poisoning, but differs in its time of incidence. In gas poisoning it is an early phenomenon, and it may, though rarely, be so complete and effective as to cause death within fifteen minutes of exposure to gas. The spasm of embolism has not been observed less than an hour after the start of the experiment, and even then it sets in gradually and only attains a maximum when death is imminent. The significance of this change is uncertain.

The work embodied in this communication was carried out at the suggestion of Mr. Joseph Barcroft, F.R.S., and under his direction. The writer has to express to him most cordial thanks for helpful advice and criticism.

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UNILATERAL ALTERATIONS IN BLOOD-PRESSURE CAUSED BY UNILATERAL PATHOLOGICAL CONDITIONS: THE DIFFERENTIAL BLOOD-PRESSURE SIGN

By EDGAR F. CYRIAX

It has long been known that local massage and exercises can reduce the local blood-pressure—hence the well-known beneficial effect of the so-called depleting or derivative exercises for heart affections and many other circulatory diseases. It has also long been appreciated that local application of heat and cold can cause local vasomotor changes of various kinds—of these facts hydrotherapy has taken every advantage. In addition it has long been realized that vasomotor changes in one arm are frequently accompanied by similar or inverse changes in the other arm. Yet it seems always to have been taken for granted that bilaterally unequal or unilateral disease, traumatism or operation, in spite of the fact that they produce unilateral sensory impulses and vasomotor reactions, do not cause differences between the blood-pressures of the two arms. In other words, the fact that normally these two pressures are identical seems to have been taken as also applicable to all pathological cases.

Personally I must confess that I had passively acquiesced in the ordinarily accepted theory that unilateral conditions did not cause unilateral blood-pressure changes, though I searched in vain for the explanation thereof. Finally, early in 1918, finding marked differences between the two radial pulses in several cases of unilateral war traumatisms, I determined to investigate the respective blood-pressures in the two arms. Employing a Martin's Riva-Rocci sphygmomanometer and Oliver's tambour, I examined thirty-six cases of arm and leg war injuries, mainly patients under the care of Mr. Mower White at the Swedish War Hospital. The results of these observations were:

Twenty-six cases showed either no differences or only small negligible ones (2–4 mm.).

Six cases showed small transient differences (6–8 mm.).

Four cases showed considerable persistent differences (up to 22 mm.). A preliminary note on these results was published in the *British Medical Journal* of August 10, 1918 (p. 132), in order that other workers on blood-pressures might take note of this possible source of error and avoid it.

Since examining the above thirty-six cases, I have taken observations on a second series of seventy-three patients, the total number of observations being 819.

[O. J. M., Jan., 1920.]

Fifteen at the Swedish War Hospital under the care of Mr. Mower White (Cases Nos. 7, 27, 37, 38, 45, 47, 48, 51, 54, 56, 61, 63, 65, 68, 73).

Thirty-four at St. Mary's Hospital under the care of Mr. Warren Low (Cases Nos. 2, 4, 8, 10, 11, 12, 19, 24, 25, 26, 28, 29, 31, 32, 33, 40, 41, 42, 44, 46, 49, 52, 53, 55, 57, 58, 59, 62, 64, 66, 69, 70, 71, 72).

Twenty-one at St. Mary's Hospital under the care of Mr. Clayton Green (Cases Nos. 1, 3, 5, 6, 9, 13, 14, 15, 16, 17, 18, 20, 21, 23, 30, 35, 36, 39, 50, 60, 67).

Two at St. Mary's Hospital under the care of Mr. T. G. Stevens (Cases Nos. 22, 34); and one from my private practice (Case No. 43).

The above cases consisted not merely of arm and leg conditions, but also those of head, thorax, and abdomen.

Technique.

All the observations were taken by myself, thus reducing the personal factor practically to nil; the apparatus employed was the one mentioned above. All the cases, excepting No. 43, were examined at practically the same hour each day and while still in bed, excepting in a few instances on their day of discharge. Whenever possible all cases were examined previous to any massage, exercises, hot-air treatment, hot-water immersion, electro-therapeutics, or painful dressings. In the two cases (Nos. 51 and 53) in which this could not be done, at least half an hour was allowed to elapse after the conclusion of such measures before taking the readings.

The observations were practically always taken on the two arms in immediate succession, commencing first with the arm dealt with last on the previous occasion. They were discontinued if disturbing psychic causes arose, the commonest being annoyance on the part of the patient at what he considered to be too frequent repetition of the readings. In order to avoid this, the observations were in most cases taken only every other day; in only one instance were they taken practically every day (No. 27).

Individual Measurements.

I give herewith the details of the seventy-three cases examined. Some of the records are of course obviously incomplete, but have been included because they show differences which were evidently not accidental or due to psychic causes. In no case does the *résumé* include the first readings, as these are notoriously unreliable. The summary of greatest differences between the readings of the two arms on any particular date includes all those of 8 or over; when none are mentioned it means that they in no case exceeded 6.

i. *Head and Neck. Case 1.* Male, aged 15. Fracture of base of skull (?) on October 8, 1918, trephined over left parietal region on October 13, when a large clot was removed. On November 19 hardly any nervous symptoms remaining

beyond left internal strabismus. B. P. observations taken on nine days between November 19 and December 7 inclusive. *Résumé*: at first decrease on the operated side as regards both maximum and minimum, which gradually diminished (average of first four observations: right side 111, 59, left side 99, 54; average of second four observations: 111, 67 and 113, 69) until the readings nearly coincided. Greatest differences: operated side, maximum −18, +10, −10, −10, +8, minimum +10, −10.

Case 2. Male, aged 43. Shrapnel wound of right eye on September 22, 1918, necessitating removal of whole eye on September 28. B. P. observations taken on seven days between October 10 and November 11 inclusive. *Résumé*: generally a decrease on the operated side as regards both maximum and minimum (average of all observations: operated side 113, 63, left side 118, 65). Greatest differences: operated side, maximum +12, −10, −10, −8.

Case 3. Female, aged 44. Osteoma of left orbit removed on November 18, 1918. B. P. observations taken on six days between November 25 and December 6 inclusive. *Résumé*: series of alternate decrease and increase in both maximum and minimum. Greatest differences: operated side, maximum +10, minimum −10.

Case 4. Female, aged 56. Carcinoma of right antrum: removal of entire right superior maxilla and hard palate on October 24, 1918. B. P. observations taken on ten days between November 8 and December 2 inclusive. Average of all readings: right side 114, 72, left side 111, 69. *Résumé*: generally increase on the operated side as regards both maximum and minimum. Greatest differences: operated side, maximum +8, minimum +16, +14.

Case 5. Female, aged 16. Large non-malignant goitre, the greater increase being on the right side. Double tonsillectomy on December 10, 1918, removal of right half of the gland on December 28, death from heart failure on December 29. B. P. observations taken on eight days between December 6 and 27 inclusive. Average of all observations: right side 107, 44, left side 105, 42. *Résumé*: tendency to increase on the right side as regards the maximum, and series of alternating increase and decrease as regards the minimum. Greatest differences: right side, minimum +16, +10. No apparent change induced by the tonsillectomy.

ii. *Thorax.*[1] *Case 6.* Male, aged 29. Attack of influenza followed by left-sided empyema, which was drained without resection of ribs on December 10, 1918. B. P. observations taken on nine days between January 2 and 19 inclusive. Average of all observations: right side 124, 76, left side 119, 75. *Résumé*: persistent increase on the healthy side as regards the maximum, series of alternate increase and decrease as regards the minimum. Greatest differences: healthy side, maximum +10, minimum +12, −8.

Case 7. Male, aged 20. Bullet through right lung on November 6, 1917; extensive pulmonary haemorrhage. Bullet found embedded below right eleventh rib; removed on February 15, 1918. B. P. observations taken on nine days between February 21 and March 24 inclusive. *Résumé*: generally an increase on the injured side as regards both maximum and minimum (average of all observations: injured side 134, 80, left side 125, 77). Greatest differences: injured side, maximum +26, +14, +14, +12, minimum +14, +8.

Case 8. Female, aged 17. Incipient tubercle of left apex and possible tubercle of the bladder. Cystoscopic examination under general anaesthesia on

[1] For mammary gland, see upper extremity *infra*.

November 14, 1918. B. P. observations taken on six days between November 8 and 22 inclusive. *Résumé*: practically persistent increase on the healthy side as regards both maximum and minimum (average of all observations: healthy side 122, 64, left side 117, 60). Greatest differences: healthy side, maximum +10, +10, minimum +12. No apparent changes from cystoscopic examination.

iii. *Abdomen.* *Case 9.* Male, aged 27. Admitted for probable duodenal ulcer; operation for same on November 27, 1918, but no ulcer discovered. B. P. observations taken on ten days between November 23 and December 17 inclusive. *Résumé*: operation followed by increase on the left side (+6) and then decrease (−18) as regards the maximum, followed by persistent increase on the left side as regards both maximum and minimum. Greatest differences: left side, maximum −18, +12, minimum +14, +10, +10, −10, −10.

Case 10. Male, aged 37. Gastro-enterostomy on November 28, 1918. Continued vomiting: reopened on December 12 but nothing found. B. P. observations taken on nine days between November 30 and December 31 inclusive. *Résumé*: effect of first operation practically nil; second operation followed by series of alternating increase and decrease. Greatest differences: left side, maximum −16, −14, −10, +8, minimum +16, −12, +10, −10, −10.

Case 11. Male, aged 53. Very prolonged operation (general anaesthesia lasting 2¾ hours), consisting of excision of half of the stomach and gastro-jejunostomy, on October 31, 1918. Second operation to free the mesentery on November 13. B. P. observations taken on fifteen occasions between November 1 and December 5 inclusive. *Résumé*: effect of first operation was a rise on the right side as regards the maximum (+8, +10) followed by a series of alternating decrease and increase as regards both maximum and minimum, apparently unaffected by the second operation. Greatest differences: right side, maximum −26, +18, −16, −10, +8, minimum −28, −14, +14, −12, +10, +10.

Case 12. Female, aged 30. Admitted for chronic appendicitis on November 14, 1918; removal of appendix on November 25. B. P. observations taken on twelve days between November 15 and December 13 inclusive. *Résumé*: before operation increase on affected side; effect of operation was a rise in the maximum (+16, +14) followed by series of alternate rise and fall. Greatest differences: operated side, maximum +12, +12, −8, minimum +10.

Case 13. Male, aged 41. Appendix abscess drained without removal of appendix on November 17, 1918. B. P. observations taken on ten days between November 23 and December 14. *Résumé*: nearly always increase on the operated side as regards the maximum (average of all observations: operated side 119, left side 114), series of alternating decrease and increase as regards the minimum. Greatest differences: operated side, maximum +12, +8, minimum −10, −8.

Case 14. Female, aged 7. Removal of appendix on November 20, 1918. B. P. observations taken on seven days between November 23 and December 7 inclusive. *Résumé*: persistent decrease on the operated side as regards the maximum and generally an increase as regards the minimum (average of all observations: operated side 95, 41, left side 102, 43). Greatest differences: operated side, maximum −12, −10, −8, minimum −12, +10, −8.

Case 15. Male, aged 60. Operation for appendicitis and double hernia on November 6, 1918. B. P. observations taken on eight days between November 23 and December 10 inclusive. *Résumé*: series of alternating increase and decrease as regards both maximum and minimum. Greatest differences: operated side, maximum −12, −8, minimum −10, −8.

Case 16. Male, aged 12. Subacute appendicitis since October 14, 1918; removal of appendix on November 21. B. P. observations taken on nine days between November 19 and December 7 inclusive. *Résumé*: previous to operation decrease (−6) in the maximum on the affected side, for four days after operation increase in both maximum and minimum (average: operated side 106, 48, left side 100, 39) on the affected side, followed by the reverse (average: right side 106, 24, left side 110, 32). Greatest differences: operated side, maximum −10, +8, minimum −20, −16, +10, +8.

Case 17. Female, aged 38. Acute appendicitis; removal of appendix on November 13, 1918. B. P. observations taken on six days between November 22 and December 4 inclusive. *Résumé*: generally an increase on the operated side as regards the maximum and decrease as regards the minimum (average of all observations: right side 133, 79, left side 125, 84). Greatest differences: operated side, maximum +20, +10, +8, minimum −20, −8.

Case 18. Female, aged 19. Attack of acute appendicitis on November 17, 1918.; removal of appendix on November 23. B. P. observations taken on ten days between November 22 and December 13 inclusive. *Résumé*: operation caused a rise on the affected side as regards both maximum and minimum (average: operated side 117, 79, left side 110, 67) which lasted four days, followed by series of alternating decrease and increase. Greatest differences: operated side, maximum −14, +10, +10, −8, minimum +18, +16, +14, −12, −12, −10.

Case 19. Female, aged 51. Subacute appendicitis; removal of appendix on November 21, 1918. B. P. observations on thirteen days between November 22 and December 28 inclusive. *Résumé*: operation usually followed by rise on the operated side (average of seven observations: operated side 97, left side 92) or equal values (on three occasions) as regards the maximum and varying effects as regards the minimum. Greatest differences: operated side, maximum +10, +8, minimum +10, −10, −8.

Case 20. Female, aged 23. Acute appendicitis; removal of appendix on November 10, 1918. B. P. observations taken on fifteen days between November 22 and December 27 inclusive. *Résumé*: series of small alternating increases and decreases as regards both maximum and minimum, with a tendency to remain slightly elevated on the operated side as regards the maximum (average of all observations: operated side 111, left side 109). Greatest differences: operated side, minimum +8, −8.

Case 21. Female, aged 47. Acute appendicitis on October 16, 1918, which became chronic; removal of appendix on December 11. B. P. observations taken on eight days between December 11 and 30 inclusive. *Résumé*: operation followed by series of alternating decrease and increase. Greatest differences: operated side, maximum −8, minimum −20, −12, +10, −10, −8.

Case 22. Female, aged 42. Removal of uterine fibroid February 17, 1918 followed by persistent pain in the right abdomen; removal of appendix, and adhesions freed, on January 3, 1919. B. P. observations taken on seven days between January 7 and 21 inclusive. *Résumé*: persistent increase on operated side as regards both maximum and minimum (average of all observations: operated side 121, 83, left side 110, 74). Greatest differences: operated side, maximum +20, +16, +10, minimum +20, +14, +10, +8.

Case 23. Female, aged 40. Operation for ventral hernia and removal of appendix on November 25, 1918. B. P. observations taken on twelve days between November 25 and December 20 inclusive. *Résumé*: operation followed by increase in both maximum and minimum, specially on the right side (average:

right side +22, +10, left side +9, +4), followed after six days by series of small alternating decrease and increase. Greatest difference: right side, maximum +16, +10, minimum −8.

Case 24. Male, aged 58. During December, 1917, removal of ring carcinoma from descending colon, short circuit of ileum into descending colon, and left-sided colotomy. Readmitted December, 1918, for constipation. B. P. observations taken on five days between December 10 and 19 inclusive. *Résumé*: persistent increase on the right side as regards the maximum (average of all observations: right side 143, left side 134), alternating increase and decrease as regards the minimum. Greatest differences: right side, maximum +10, +10, +8, +8, minimum +8.

Case 25. Male, aged 50. Removal of hydatid of liver (incision in middle line) on November 4, 1918. B. P. observations taken on twenty-one days between November 7 and December 14 inclusive. *Résumé*: series of alternating increase and decrease as regards both maximum and minimum, tending gradually to diminish. Greatest differences: right side during November 7–16, maximum +14, −12, during November 18 to December 14, −8.

Case 26. Female, aged 36. Right floating kidney diagnosed August, 1918; nephrorrhaphy November 25. B. P. observations taken on twelve days between November 22 and December 16 inclusive. *Résumé*: operation followed by fairly persistent increase on the operated side as regards the maximum (average of all observations: operated side 125, left side 122) and alternating decrease and increase as regards the minimum. Greatest differences: operated side, maximum +10, minimum +14, −12, +10, −8.

Case 27. Male, aged 35. Operation for double inguinal hernia during June, 1917; right hernia recurred; second operation on November 1, 1918; peritoneal pouch found. B. P. observations taken on twenty-six days between October 31 and November 30, and again on December 2, 5, and 17 inclusive. *Résumé*: persistent decrease on the operated side as regards the maximum until November 22 (average of eighteen observations during this period: operated side 116, left side 122), followed by no difference between the two until December 17 (average of ten observations during this period: operated side 121, left side 122), and alternate increase and decrease as regards the minimum. Greatest differences: unoperated side, maximum +22, +16, +10, +10, +10, +8, +8, +8, minimum −14, +12, +12, +8, −8, −8.

Case 28. Female, aged 42. Radical cure for right femoral hernia on November 20, 1918. B. P. observations taken on six days between November 22 and December 6 inclusive. *Résumé*: generally an increase on the unoperated side as regards both maximum and minimum (average of all observations: unoperated side 124, 82, right side 120, 75). Greatest differences: unoperated side, minimum +20, +8.

Case 29. Female, aged 69. Operation for second time for left strangulated femoral hernia on November 4, 1918. B. P. observations taken on ten days between November 8 and December 2 inclusive. *Résumé*: generally an increase on the operated side as regards both maximum and minimum (average of all observations: operated side 156, 98, right side 150, 96). Greatest differences: operated side, maximum +16, +14, +14, +14, +10, minimum +10, −8.

Case 30. Male, aged 64. Left-sided colotomy for intestinal obstruction on November 23, 1918. B. P. observations taken on sixteen days between November 26 and January 10 inclusive. *Résumé*: preliminary rise on the operated side

as regards the maximum (average of first four observations: operated side 121, right side 115), followed by series of small alternating increase and decrease. Greatest differences: operated side, maximum +8, minimum +8, −8, −8.

Case 31. Male, aged 56. Excision of rectum for malignant disease on September 17, 1918. B. P. observations taken on thirteen days between October 22 and November 23 inclusive. *Résumé*: series of alternating increase and decrease as regards both maximum and minimum. Greatest differences: right side, maximum −16, +10, +8, minimum +16, +14, +8, +8.

Case 32. Male, aged 44. Neurasthenia: operation for prolapse of rectum during July, 1917; readmitted for retention of urine during December, 1918. Persistent catheterization December 13–27. B. P. observations taken on six days between December 14 and 31 inclusive. *Résumé*: nearly always an increase on the right side as regards both maximum and minimum (average of all observations: right side 133, 79, left side 122, 70). Greatest differences: right side, maximum +24, +22, +18, minimum +16, +12, +12.

Case 33. Female, aged 34. Abortion on September 20, 1918, followed by pelvic cellulitis. September 30, laparotomy, nothing special found; superficial abscess below lower right ribs drained by lumbar incision. B. P. observations taken on nine days between November 8 and 29 inclusive. *Résumé*: series of alternating increase and decrease as regards both maximum and minimum. Greatest differences: right side, maximum +10, +8, −8, minimum +10, −8.

Case 34. Female, aged 42. Menorrhagia for many years; subtotal hysterectomy on January 3, 1919; uterus found to have three subperitoneal fibroids. B. P. observations taken on seven days between January 7 and 21 inclusive. *Résumé*: increase in the maximum on the right side and decrease in the minimum (average of all observations: right side 119, 71, left side 114, 73). Greatest differences: right side, maximum +10.

Case 35. Male, aged 26. Progressive enlargement during eighteen months of right testicle; removal of same on December 11, 1918. B. P. observations taken on eleven days between December 12 and January 3 inclusive. *Résumé*: operation followed by marked fall equally on both sides as regards the maximum (−18) with subsequent rise to the original also equally on both sides, with ensuing series of alternating increase and decrease. Greatest differences: operated side, maximum +12, +12, +10, minimum −14, −10, −8.

Case 36. Male, aged 67. Suprapubic lithotomy for removal of large calculus (12 oz.) on November 27, 1918. B. P. observations taken on fifteen days from November 23 to December 30 inclusive. *Résumé*: series of alternating increase and decrease as regards both maximum and minimum. Greatest differences: right side, maximum +10, +10, −8, minimum −16, −16, −14, −10, −10, +8.

Case 37. Male, aged 28. Shrapnel wound of anterior abdominal and thoracic wall, entering on right side and becoming embedded below left ribs, exposing the pericardium, on October 7, 1918. Bullet extracted October 8. B. P. observations taken on nine days between October 19 and November 22. *Résumé*: generally an increase on the right side as regards both maximum and minimum (average of all observations: right side 121, 67, left side 117, 64). Greatest differences: right side, maximum +8, +8, minimum +8.

Case 38. Male, aged 28. Small lipoma on left side of umbilicus, inflamed since about October 26, 1918, removed on November 16. B. P. observations taken on six days between November 20 and December 3 inclusive. *Résumé*: preliminary increase on operated side as regards both maximum and minimum (average of first three readings: operated side 115, 77, right 107, 67), with return

to the normal, the last two readings being identical. Greatest differences: operated side, maximum +8, minimum +16, +12.

Case 39. Male, aged 14. Pain in right lower thorax for one month: abscess below right twelfth rib drained on December 2, 1918. B. P. observations taken on twelve days between November 30 and December 30. *Résumé*: operation followed by decrease on that side, specially as regards the minimum (−16), with ensuing series of alternating increase and decrease. Greatest differences: operated side, maximum +12, −10, −10, minimum −16, +14, −8, −8.

iv. *Upper Extremity.*[2] *Case 40.* Female, aged 72. Removal of atrophic scirrhus from left mammary gland on October 28, 1918. B. P. observations taken on nine days between November 8 and 29 inclusive. *Résumé*: generally an increase on the healthy side as regards the maximum (average of all observations: healthy side 129, left side 121), and series of alternating increase and decrease as regards the minimum. Greatest differences: healthy side, maximum +18, +18, +12, +10, minimum +20, −18, +12, +12.

Case 41. Female, aged 50. Abscess of left mammary gland opened on November 21, 1918, a second small collection of pus opened on December 9. B. P. observations taken on twelve days between November 22 and December 18 inclusive. *Résumé*: first operation followed by slight rise on the unoperated side as regards the maximum and slight fall as regards the minimum (average of first three observations: unoperated side 129, 81, left side 125, 83), second operation followed by persistent increase on the operated side (average of four observations: operated side 122, 83, left side 114, 74). Greatest differences: operated side, maximum +10, minimum +18, +10, +8, +8.

Case 42. Male, aged 23. Shrapnel wound of right shoulder on August 31, 1918; attempt to extract the missile unsuccessful. Wound alternately breaking down and healing. B. P. observations taken on sixteen days between October 17 and January 8 inclusive. *Résumé*: series of alternating increase and decrease. Greatest differences: uninjured side, maximum +12, +10, +8, minimum −14, −10, −10.

Case 43. Male, aged 60. Dislocation of left humerus on May 23, 1918, reduced same day. Functional restoration practically complete by June 12. B. P. observations taken on six days between May 30 and June 12 inclusive, and again on July 23 and October 17. *Résumé*: during the first period generally an increase on the injured side (average of all observations: injured side 144, 90, right side 136, 88), during the last two dates no change. Greatest differences: injured side, maximum +18, +12, +10, +8, −8, minimum +8.

Case 44. Male, aged 25. Through and through gunshot wound of right shoulder, removing greater part of deltoid but not damaging the joint, on August 27, 1918. Considerable weakness of arm remaining. B. P. observations taken on twelve days between October 10 and November 11 inclusive. *Résumé*: series of alternating increase and decrease. Greatest differences: injured side, maximum +12, −12, +10, +8, −8, −8, minimum −12, −10, −10, −10, +8, −8.

Case 45. Male, aged 20. Bullet wound with resultant compound fracture of right humerus and complete severance of musculo-spiral nerve on March 21, 1918. Nerve suture performed on September 19, 1918. B. P. observations taken on four days between July 2 and September 18 inclusive, and after the wound was healed on five days between October 24 and November 12 inclusive. *Résumé*: series of alternate increase and decrease. Greatest differences: uninjured side, maximum +22, +16, −10, −8, minimum −18, +10, −10, +8.

[2] For the sake of convenience I have included the mammary gland under this heading.

Case 46. Male, aged 25. Fracture of both bones of right forearm on November 11, 1918. B. P. observations taken on six days between December 5 and December 16 inclusive. *Résumé*: series of alternate increase and decrease. Greatest differences: injured side, minimum +20, +8.

Case 47. Male, aged 31. Grenade wound embedding many pieces of metal in right arm and forearm on October 29, 1918. One large piece in forearm removed under complete anaesthesia on November 16. B. P. observations taken on six days between November 6 and 22 inclusive. *Résumé*: previous to operation increase on the injured side as regards the maximum (average of two observations: injured side 130, left side 119), after the operation the reverse (average of three observations: injured side 115, left side 123); decrease on the injured side as regards the minimum throughout (average of five observations: injured side 69, left side 74). Greatest differences: injured side, maximum +16, −12, minimum −10.

Case 48. Male, aged 35. Several pieces of shrapnel embedded in left forearm on September 29, 1918. One large piece removed under local anaesthesia on October 9. B. P. observations taken on five days between October 7 and 29 inclusive. *Résumé*: series of alternate increase and decrease as regards both maximum and minimum. Greatest differences: injured side, maximum +12, +10, −10, minimum −10, −8.

Case 49. Male, aged 30. Gunshot wound of left forearm on August 28, 1918. Wound nearly healed by October 14. B. P. observations taken on eight days between October 14 and November 11 inclusive. *Résumé*: series of alternate increase and decrease as regards both maximum and minimum. Greatest differences: uninjured side, maximum +14, +10, +8, minimum +14, +8.

Case 50. Female, aged 18. Right forearm and hand crushed in machinery on November 13, 1918. B. P. observations taken on six days between November 22 and December 6 inclusive. *Résumé*: persistent increase on injured side, specially as regards the minimum (average of five observations: injured side 125, 80, left side 118, 65). Greatest differences: injured side, maximum +14, +12, +8, minimum +26, +18, +18, +12.

Case 51. Male, aged 36. Gunshot wound of left hand, fracturing fifth metacarpal, on November 4, 1918. B. P. observations taken on nine days between November 8 and December 7 inclusive, and once again on December 28. *Résumé*: preliminary decrease on injured side as regards the maximum (average of three observations: injured side 108, right side 121), followed by series of alternate increase and decrease. Greatest differences: uninjured side +14, +12, −12; right side −22, −8, −8, −8.

Case 52. Male, aged 32. Gunshot comminuted fracture of first phalanx of second finger of left hand on August 27, 1918; considerable functional disability remaining. B. P. observations taken on eleven days between October 10 and November 11 inclusive. *Résumé*: series of alternate increase and decrease. Greatest differences: injured side, maximum −16, +14, −12, −8, minimum, −10.

Case 53. Male, aged 35. Slight wound of second finger of right hand on April 30, 1918; septic inflammation necessitating amputation one week later. Wound quite healed by October 12, but stiffness and weakness of hand remaining. B. P. observations taken on eighteen days between October 12 and December 5 inclusive. *Résumé*: series of alternate increase and decrease. Greatest differences: injured side, maximum −14, −14, −14, +12, −12, −12, −10, −10, −10, −8, minimum −24, −22, −20, −10.

v. *Lower Extremity. Case 54.* Male, aged 32. Gunshot flesh wound of the left buttock on October 15, 1918. B. P. observations taken on five days between October 19 and November 7 inclusive. *Résumé*: persistent decrease on the injured side as regards the maximum (average of all observations: injured side 112, right side 120), varying results as regards the minimum. Greatest differences: injured side, maximum −10, −10.

Case 55. Male, aged 25. Wound of left thigh during March, 1918, followed by thrombosis during May; wound broke down on November 1, now healing well. B. P. observations taken on seven days between November 14 and December 3 inclusive. *Résumé*: apart from an increase of 12 in the minimum in the affected thigh on one occasion, only very slight negligible differences.

Case 56. Male, aged 23. Fracture of left humerus and left femur during October, 1917; the former healed fairly soon, but the latter did not; plating performed during February, 1918, and removed October 22, 1918. B. P. observations taken on sixteen days between October 24 and December 19 inclusive. *Résumé*: series of alternate increase and decrease. Greatest differences: injured side, maximum +16, −12, −10, −8, −8, minimum +14, +10, +10, −10, −10, −8.

Case 57. Male, aged 25. Gunshot wound below Poupart's ligament on the left side on August 31, 1918, with resultant aneurysm of the femoral artery. Wound healed by October 12. B. P. observations taken on eighteen days between October 12 and December 3 inclusive, and on eight days between January 1 and 27 inclusive. *Résumé*: preliminary decrease on the injured side as regards the maximum and increase as regards the minimum (average of first eleven observations: injured side 103, 35, right side 114, 27), followed by series of alternate increase and decrease. Greatest differences: injured side, maximum −24, −14, −14, −12, −12, +10, minimum +28, +22, +22, −22, +20, +18, +16, +14, +10, +10, +8, +8, +8.

Case 58. Male, aged 38. Mild gunshot wound of left elbow and severe one of right thigh. Both wounds healed by September 28, but right drop-foot persisting. B. P. observations taken on six occasions between October 14 and November 12. *Résumé*: slight negligible variations only.

Case 59. Male, aged 38. Multiple gunshot wounds of the right thigh on August 27, 1918. B. P. observations taken on ten days between October 10 and November 11 inclusive. *Résumé*: persistent increase on the injured side as regards both maximum and minimum (average of all observations: injured side 130, 83, left side 124, 79). Greatest differences: injured side, maximum +14, +10, +8, minimum −10, −8.

Case 60. Male, aged 14. Fracture of left femur on October 12, 1918, healing in bad position, re-broken and re-set on November 19. B. P. observations taken on sixteen days between November 19 and December 30 inclusive. *Résumé*: operation followed by slight rise as regards the maximum (+4) on the injured side and marked fall as regards the minimum (−26), with subsequent slight variations in the maximum, but persistent rise as regards the minimum (average of fourteen observations: injured side 59, right side 47). Greatest differences: injured side, maximum −12, minimum −26, +24, +22, +18, +18, +14, +10, +10, +8, +8.

Case 61. Male, aged 24. Shrapnel wound of left loin and right thigh on September 9, 1918. The latter healed by October 18, but the former not yet quite healed by December 10. B. P. observations taken on twelve days between September 27 and December 10 inclusive. *Résumé*: persistent increase on the

right side as regards the maximum (average of all observations: right side 118, left side 114), and series of alternating increase and decrease as regards the minimum. Greatest differences: right side, maximum +10, +8; minimum +20, −14, −10.

Case 62. Male, aged 17. Tubercular psoas abscess on the right side, opened on September 16, 1918, through the abdomen. B. P. observations taken on sixteen days between November 19 and December 31 inclusive. *Résumé*: generally an increase on the operated side as regards the maximum (average of all observations: operated side 116, left side 112), series of alternating increase and decrease as regards the minimum. Greatest differences: affected side, maximum +16, +16, +12, minimum +10, −8, −8.

Case 63. Male, aged 33. Shrapnel wound of left knee, removing a portion of the patella, on October 1, 1918. B. P. observations taken on seventeen days between October 19 and December 17 inclusive. *Résumé*: series of alternating increase and decrease. Greatest differences: injured side, maximum +14, +10, −10, minimum +16, +10, −10, −10, +8, +8.

Case 64. Male, aged 35. Gunshot injury to left knee; knee-joint excised August 12, 1918. B. P. observations taken on sixteen days between October 10 and December 9. *Résumé*: series of alternating increase and decrease. Greatest differences: uninjured side, maximum +12, +12, +10, +8, +8, −8, minimum +16, +10, −10, +8, −8.

Case 65. Male, aged 25. Right foot shot away; amputation below knee on August 9, 1918. Head of fibula excised on October 22. B. P. observations taken on twenty days between August 29 and November 13 inclusive. *Résumé*: preliminary increase on the injured side as regards the maximum and decrease as regards the minimum (average of first three observations: injured side 123, 60, left side 117, 64), followed by slight variations only; second operation caused persistent increase on the injured side as regards the maximum, but very little change as regards the minimum (average of seven observations: injured side 122, 61, left side 115, 63), last two readings equal. Greatest differences: injured side, maximum +14, +12, +12, +10, +10, +10, −10, −8, minimum +12, +10, −8.

Case 66. Male, aged 38. Gunshot wound partially shattering right tibia during August, 1915; wound has been healing up and breaking down ever since. B. P. observations taken on nineteen days between October 10 and November 27 inclusive. *Résumé*: generally persistent increase on the injured side as regards the maximum (average of all observations: injured side 123, left side 116), series of alternate increase and decrease as regards the minimum. Greatest differences: injured side, maximum +28, +16, +14, +14, +12, +10, +8, +8, minimum +14, +10, +10, +10.

Case 67. Female, aged 13. Persistent pain in left tibia during two years; portion of dead bone removed on November 30, 1918. B. P. observations taken on twenty-three days between November 22 and December 19 inclusive. *Résumé*: series of alternate increase and decrease as regards the maximum, generally an increase (sometimes very marked) on the operated side as regards the minimum (average of all observations: operated side 43, right side 33). Greatest differences: operated side, maximum +10, +10, −8, minimum +32, +28, +28, +26, +20, +18, +18, +12, +10, +8, +8.

Case 68. Male, aged 21. Gunshot wound through the left calf, damaging the fibula, on October 15, 1918. B. P. observations taken on sixteen days between October 25 and December 10 inclusive. *Résumé*: generally a slight

decrease on equal readings on the injured side as regards the maximum and series of alternate increase and decrease as regards the minimum. Greatest differences: injured side, maximum −12, minimum +18, −18, −14, −10, +8, +8.

Case 69. Male, aged 27. Through and through gunshot wound of left calf on August 27, 1918; inner wound not healing well. B. P. observations taken on twelve days between October 10 and November 11 inclusive. *Résumé*: nearly always a decrease on the injured side as regards both maximum and minimum (average of all observations: injured side 105, 63, right side 113, 74). Greatest differences: injured side, maximum −18, −12, −12, −10, −8, minimum −12, −12, +8.

Case 70. Male, aged 19. Gunshot wound of left foot on August 27, 1918; functional disability remaining. B. P. observations taken on eleven days between October 10 and November 11 inclusive. *Résumé*: series of alternate increase and decrease as regards both maximum and minimum. Greatest differences: injured side, maximum +12, −10, −8, minimum +12, −10, −8.

Case 71. Male, aged 32. Gunshot wound of right ankle on April 9, 1917, wound broke down July, 1918; healed once more by September, 1918. B. P. observations taken on twelve days between October 10 and November 11 inclusive. *Résumé*: persistent increase on the injured side as regards the maximum (average of all observations: injured side 114, left side 106), and series of alternate increase and decrease as regards the minimum. Greatest differences: injured side, maximum +16, +12, +10, +10, +8, minimum +18, +10, +8.

Case 72. Male, aged 40. Minor shrapnel wound of right calf and bad shrapnel wound of right foot, necessitating immediate amputation below the astragalus on September 1, 1918; three incisions for drainage near the ankle made on October 22, 1918. B. P. observations taken on fifteen days between October 12 and December 5 inclusive. *Résumé*: series of alternate increase and decrease as regards both maximum and minimum. Greatest differences: injured side, maximum +14, +12, −12, −10, +8, −8, minimum +12, +10, +10, −10, −10.

Case 73. Male, aged 31. Fracture of third and fourth left metatarsals from a piece of shrapnel on November 8, 1918. B. P. observations taken on seven days between November 20 and December 17. *Résumé*: generally slight decrease on the injured side as regards the maximum (average of all observations: injured side 99, right side 102), series of slight alternate increase and decrease as regards the minimum.

Results.

Naturally a much larger number of cases will have to be investigated before definite conclusions can be drawn, but as far as can be ascertained at present, the following may be postulated: In unilateral or bilaterally unequal conditions, whether from trauma or operation, and irrespective of site (head, limbs, or trunk), the blood-pressures in the two arms nearly always show marked differences. On the other hand, they are not usually encountered in operations confined to the middle line or performed equally on both sides of the body. In order to have a convenient term for referring to the differences when they exist, I have applied the phrase 'The differential blood-pressure sign'.

The manner in which the differences between the two arms occur are very similar in both trauma and operation, namely as follows:

(*a*) As regards the maximum pressures. During the acute stage of the trauma or for the first day or two after operation, the maximum pressure is higher in the arm on the affected side. This soon gives way to the reverse, so that it becomes higher in the other arm. If convalescence is normal and rapid both pressures return fairly quickly to their original amounts, thus again coinciding. If convalescence is delayed, this gives rise to a series of alternating increases and decreases, which generally tend progressively to diminish in intensity.

(*b*) As regards the minimum pressures. These tend to vary similarly to the maximum, but independent changes are very common. The effect of these is to cause wide variations in the pulse pressures.

It is generally impossible to decide whether a higher reading on one side is the result of a unilateral increase on that side or of a unilateral decrease on the other, or a combination of the two. This could only be decided if a prolonged series of observations had been taken previous to the trauma or operation that caused the differences, and this has of course not been done in the vast majority of cases.

In view of the fact that series of alternating increase and decrease are very common, it is quite probable that some of the first twenty-six cases originally examined (see above), which were considered not to exhibit the differential blood-pressure sign, may in reality have had it, but that it passed unnoticed because I only took very few observations on them, and may just have done so when a descent in one arm coincided with an ascent in the other.

The extent of the changes encountered (excluding the first readings) were as follows:

(*a*) Maximum pressure:

Differences of	28	occurred	once in 1 case
	26		twice in 2 cases
	24		3 times in 2
	22	2	3
	20	2	2
	18	8	7
	16	16	15
	14	24	17
	12	45	33
	10	69	61

(*b*) Minimum pressure:

Differences of	32	occurred	once in 1 case
	28		4 times in 3 cases
	26	3	3
	24	2	2
	22	6	3
	20	11	11
	18	13	10
	16	13	12
	14	20	19
	12	23	19
	10	68	59

Considered more in detail the results were as follows:

Differences of 12 and upwards between both maximum and minimum pressures (not of necessity occurring on the same day) were found in the following thirty-three cases:

Case No.	Maximum.	Minimum.	Nature of case.
66	28, 16, 14, 14, 12	14	Gunshot wound of tibia
11	26, 18, 16	28, 14, 14, 12	Excision of half of stomach and gastro-jejunostomy
7	26, 14, 14, 12	14	Bullet through lung
32	24, 22, 18	16, 12, 12	Neurasthenia, old operation for prolapse of rectum, retention of urine
57	24, 14, 14, 12, 12	28, 22, 22, 22, 20, 18, 16, 14	Traumatic aneurysm of thigh
27	22, 16	14, 12, 12	Operation for inguinal hernia
45	22, 16	18	Severance of musculo-spiral nerve
22	20, 16	20, 14	Removal of appendix
17	20	20	Removal of appendix
40	18, 18, 12	20, 18, 12, 12	Removal of mammary scirrhus
69	18, 16, 12, 12	12, 12	Gunshot wound of calf
9	18, 12	14	Operation for duodenal ulcer
10	16, 14	16, 12	Gastro-enterostomy
56	16, 12	14	Fracture of femur
71	16, 12	18	Old gunshot wound of ankle
31	16	16, 14	Excision of rectum
53	14, 14, 14, 12, 12, 12	24, 22, 20	Amputation of one finger
65	14, 12, 12	12	Amputation below knee
51	14, 12, 12	22	Gunshot wound of hand
72	14, 12, 12	12	Partial amputation of foot
50	14, 12	26, 18, 18, 12	Crush of forearm and hand
18	14	18, 16, 14, 12, 12	Removal of appendix
63	14	16	Shrapnel wound of knee
49	14	14	Gunshot wound of forearm
35	12, 12	14	Removal of testicle
44	12, 12	12	Gunshot wound of shoulder
64	12, 12	16	Excision of knee
60	12	26, 24, 22, 18, 18, 14	Re-fracture of femur
39	12	16, 14	Abscess below twelfth rib
68	12	18, 18, 14	Gunshot wound of calf
42	12	14	Shrapnel wound of shoulder
70	12	12	Gunshot wound of foot
14	12	12	Removal of appendix

Differences of 12 and upwards between the maximum pressures, those between the minimum pressures in no case exceeding 10, were found in the following fourteen cases:

Case No.	Maximum.	Nature of case.
43	18, 12	Dislocation of humerus
1	18	Trephining
62	16, 16, 12	Psoas abscess opened
29	16, 14, 14, 14	Operation for strangulated femoral hernia
52	16, 14, 12	Fracture of one phalanx
47	16, 12	Shrapnel wounds of forearm
23	16	Operation for ventral hernia and appendix
25	14, 12	Removal of hydatid of liver
59	14, 12	Gunshot wounds of thigh
12	12, 12	Removal of appendix
2	12	Removal of one eye
13	12	Appendix abscess drained
15	12	Operation for appendicitis and double hernia
48	12	Shrapnel wounds of forearm

Differences of 12 and upwards between the minimum pressures, those between the maximum in no case exceeding 10, were found in the following fifteen cases:

Case No.	Minimum.	Nature of case.
67	32, 28, 28, 26, 20, 18, 18, 12	Resection of part of tibia
16	20, 16	Removal of appendix
61	20, 14	Shrapnel wound of thigh
21	20, 12	Removal of appendix
28	20	Operation for femoral hernia
46	20	Fracture of both bones of the forearm
41	18	Operation for mammary abscess
36	16, 16, 14	Suprapubic lithotomy
4	16, 14	Removal of superior maxilla
38	16, 12	Removal of lipoma of abdominal wall
5	16	Enlargement of thyroid gland
26	14, 12	Nephrorrhaphy
6	12	Empyema
8	12	Tubercle of one apex (?)
55	12	Wound of thigh: old thrombosis

Immediate effect of the actual operation. This is as a rule very difficult to ascertain, because the condition of the patient during the ensuing forty-eight hours after the operation is often such that it would either not be justifiable to take any observations or else such that psychic disturbance would arise were they attempted which would render them inaccurate. In the following cases the observations taken showed that as regards the maximum pressure the immediate effect of operations was as follows:

Case No.	Operation.	Result.
12	Removal of appendix	Very little change
26	Nephrorrhaphy	Increase on the operated side
27	Operation for inguinal hernia	Decrease on the operated side
33	Drainage of abscess below twelfth rib	Decrease on the operated side
36	Suprapubic lithotomy	Very little change
65	Excision of head of fibula in previous amputation below knee	Increase on the operated side
67	Excision of portion of tibia	Very little change

Remote effect of the actual operation or trauma. The commonest one encountered was a series of alternating increase and decrease; next in order came a prolonged increase in the maximum pressure on the affected side and least commonly a decrease in the same. As regards the two latter, they were present in the following cases:

(*a*) Increase on affected side:

Case No.	Nature of case.
4	Removal of superior maxilla
5	Enlargement of thyroid gland
7	Bullet extraction below twelfth rib
12	Removal of appendix
13	Appendix abscess drained
17	Removal of appendix
18	Removal of appendix
19	Removal of appendix
20	Removal of appendix
23	Removal of appendix and operation for ventral hernia
26	Nephrorrhaphy
38	Removal of lipoma of abdominal wall
50	Crush of forearm and hand
59	Gunshot wounds of thigh
62	Psoas abscess drained
65	Excision of head of fibula
66	Old gunshot wound of tibia
71	Old gunshot wound of ankle

(*b*) Increase on healthy side:

Case No.	Nature of case.
1	Trephining
2	Removal of one eye
8	Tubercle of one apex (?)
9	Operation for duodenal ulcer
14	Removal of appendix
27	Operation for inguinal hernia
28	Operation for femoral hernia
37	Bullet wound exposing pericardium
54	Gunshot wound of hip
57	Traumatic aneurysm of thigh
61	Shrapnel wound of loin
68	Gunshot wound of calf
69	Gunshot wound of calf

An increase in the maximum pressure on one side in middle line operations was found in two instances, namely in Case 32 (neurasthenia, old operation for prolapse of rectum, retention of urine) and Case 34 (subtotal hysterectomy for fibroids).

No differences at all were encountered in only one case (No. 58), and only present on one occasion in one other case (No. 55).

The mechanism by which the differential blood-pressure sign is produced. There are several factors which may be at work with varying intensity at the same time, and this is in my opinion the reason why such varying results are obtained. These factors are:

(1) Sensory stimuli due to the trauma or operation.

(2) In the case of operation, removal of already existing stimuli from pain, tension, muscular spasm, &c.

(3) The vaso-dilatation of the mechanism of repair which is situated in the peripheral nerves.

(4) Changes in impulses from muscles, &c., in consequence of their atrophy, of disuse, or true degeneration.

(5) A psychic effect due to the patient's attention continually being drawn to the injured area.

Now although it is easy to understand why a local arm trauma or operation on one arm can induce local blood-pressure changes in that member, and thereby reflexly in the other arm, it is difficult to see why these result from local head, trunk, and leg conditions, unless we presume that the two halves of the vaso-motor system are much more independent of one another than is generally supposed.

As far as I can judge at present, the course and extent of the differential blood-pressure sign does not appear to be affected by general anaesthesia as induced by ether open, ether closed, gas and ether, ether and chloroform, chloroform alone, and gas alone. It is encountered in patients of all ages and in both sexes. A comparison with the pulse and respiration records shows that it in no way follows their variations. Nor does it appear to be influenced by menstruation, removal of stitches, administration of drugs or vaccines, change of posture or exercise, or a moderate degree of pyrexia.

When the matter has been more fully investigated, I think that the differential blood-pressure sign will prove of considerable value not only as a diagnostic but also as a prognostic.

Before concluding I wish to express my heartiest thanks to all the physicians and surgeons mentioned who so kindly placed their available material at my disposal.

Summary.

1. The differential blood-pressure sign (namely differences between the readings in the two arms) is nearly always present in unilateral or bilaterally unequal traumatisms or operations.

2. As regards the maximum pressures, differences of 10 mm. are found in about 83 per cent., and of 20 mm. or over in about 12 per cent. of all cases. As regards the minimum pressures, similar differences are found respectively in 81 per cent. and 20 per cent.

3. In the conditions mentioned under (1), blood-pressure readings taken from only one arm are very liable to lead to totally erroneous conclusions.

NOTE. Since writing the above I have examined a further series of 200 cases which fully confirm what I have already found; I hope shortly to publish the results. Observations on the differential blood-pressure sign in phthisical patients are also being taken by my brother, Dr. R. J. Cyriax; a preliminary note has already been published by him in the *British Medical Journal* of 1918, ii. 572–3, and a fuller statement in the *British Journal of Tuberculosis*, 1919, xiii. 73–77.

A NUMERICAL MEASUREMENT OF DYSPNOEA

By G. H. HUNT and D. DUFTON

With Plate 4

I. *Introductory.*

The object of the research in this paper was to find a method of measuring more accurately than by mere observation the amount and duration of a person's dyspnoea on exercise, and to judge from this measurement the amount of disability, if any, from which he was at that time suffering. In order that the values obtained might be in effect a measurement of the patient's deviation from the normal, we found it necessary to carry through a series of experiments on normal healthy students, with the object of finding out the degree of dyspnoea produced by a given exercise in a healthy man. We started with the assumption that the breathlessness shown by the same individual over any given exercise was approximately the same from time to time, provided that there was no marked alteration in his physical condition. Our object was then to find out, from the figures obtained, how this constancy could be best expressed.

II. *Method.*

The method used in investigating the respiration was as follows: The ventilation at rest was determined by making the patient breathe through a meter, and the amount noted for each minute. The ventilation during and after exercise, which was done on a Martin's bicycle ergometer, was measured by collecting air into Douglas bags, since the flow of air was too rapid to be susceptible of accurate measurement when passed directly through the meter. The respiration rate was taken simultaneously so that the depth of respiration could be calculated. The arrangement of the apparatus is shown in Fig. 1, A and B (Plate 4). We found that the resting ventilation from minute to minute varied slightly at different times in the same individual. We therefore determined the average resting ventilation over a period of from four to twelve minutes. By this means any irregularities in ventilation, such as an increase per minute when the valve is first put on, could be excluded.

TABLE I.

		Total Ventilation.					Respirations.			
		Resting.	During.	1st Min.	Total.	Dyspnoea Ratio.	Resting.	During.	1st Min.	Total.
1st exercise,3,900 ft. lb. in 1½ mins.	G. H. H.	4·76	18·90	10·55	21·27	1·12	9	15	12	33
		5·24	21·75	12·00	24·93	1·19	9	15	12	36
		5·50	23·02	15·85	25·10	1·14	9	17	15	39
		5·53	24·35	12·80	25·00	1·13	9	19	13	37
		5·76	20·00	12·45	23·90	1·04	9	20	11	35
		6·80	24·00	12·85	28·20	1·04	9	—	12	40
	Variation	30 %	21 %	34 %	25 %	13 %				
	H. C.	4·89	22·49	12·95	24·55	1·25	6	16	10	24
		5·47	23·00	11·70	26·25	1·20	6	16	10	29
		5·77	24·20	12·70	26·48	1·15	6	15	10	27
		5·77	24·90	10·90	27·19	1·18				
		5·87	—	—	26·35	1·12				
	Variation	17 %	10 %	16 %	10 %	8 %				
	P. K.	6·87	27·50	15·15	30·55	1·11	17	—	—	80
		9·12	28·20	20·25	37·10	1·02	—	32	26	105
		9·56	28·10	16·90	39·55	1·03				
		10·23	36·50	20·25	37·10	1·02	19	32	24	83
		10·23	36·45	15·45	44·00	1·07	—	38	26	114
	Variation	33 %	25 %	25 %	23 %	8 %				
2nd exercise,6,470 ft. lb. in 1¼ mins.	G. H. H.	5·54	29·17	19·28	29·15	1·60				
		5·04	—	20·60	29·62	1·46	9	20	20	39
		5·17	32·10	24·75	35·25	1·55	9	19	22	45
		5·41	33·80	25·25	31·85	1·48	9	24	22	43
		5·46	38·50	22·70	30·13	1·38				
		5·76	27·70	26·70	34·52	1·50				
		5·86	31·75	22·60	31·37	1·35				
		6·05	21·16	20·45	33·53	1·38	9	15	17	43
		6·31	—	20·10	36·55	1·45	9	16	14	42
	Variation	28 %	32 %	28 %	20 %	16 %				
	H. C.	4·95	31·50	18·75	35·10	1·78	6	19	11	31
		4·96	—	22·63	35·04	1·76	4	13	11	24
		5·05	27·65	24·35	38·05	1·88	5	15	11	34
		5·07	34·00	19·60	33·00	1·64				
		5·07	28·60	22·85	35·65	1·76	—	16	12	35
		5·09	35·30	24·05	35·25	1·73	6	18	11	33
		5·22	26·02	25·30	39·45	1·89	—	15	13	31
		5·51	30·32	23·57	37·25	1·69	5	19	11	28
		5·58	37·15	19·85	37·65	1·68	6	20	11	30
		5·62	—	20·87	33·70	1·55	6	14	11	30
		5·70	31·25	21·40	37·90	1·66	6	16	12	33
		5·94	32·41	23·70	39·37	1·66	6	18	13	32
		10·72	33·50	23·50	67·23	1·58	14	29	15	68
	Variation	54 %	30 %	26 %	51 %	18 %				
	P. K.	6·99	34·85	26·20	41·35	1·48	18	27	23	82
		9·08	25·20	24·80	49·40	1·36				
		9·20	29·70	26·65	57·00	1·55	—	32	26	111
	Variation	24 %	28 %	7 %	27 %	12 %				

III. *Preliminary Experiments.*

We first examined three healthy men at different times over two exercises differing in severity and duration. We considered the total ventilation and respiratory rate over four different periods:

(1) At rest. (2) During exercise. (3) During the first minute after exercise. (4) During the second, third, fourth, and fifth minutes after exercise.

The results are given in Table I. (The meaning of 'Dyspnoea ratio' in column 7 will be explained later.)

The figures for the four periods vary considerably for the same man at different times, and vary very widely for the three individuals. So great are the variations that it is clearly impossible to consider any single value for any period even approximately constant for an average healthy man.

In many pathological conditions dyspnoea after exertion persists much longer than normal; if a healthy man and a patient with heart disease go up a flight of stairs together, it is after the exercise is over that the difference in their breathing is most obvious; soon after reaching the top the former is breathing quietly, while the latter is still panting. We thought it probable, therefore, that the time taken for the breathing to return after exercise to the condition at rest, being different in healthy and gassed men, might afford a suitable measurement of the difference in their degree of dyspnoea. Accordingly we tried to measure the time taken for the ventilation to return to its volume at rest after a given exercise. This was found unsatisfactory for the following reason. The total ventilation of a healthy man at rest, although approximately constant for successive periods of three minutes or longer, varies considerably in individual minutes. This is due partly to slight variations in the rate of respiration, but more to variations in depth; it is quite usual for a deep sighing respiration, followed by one or more shallower breaths, to occur once or even twice a minute. Should the deep breath occur just at the end of one minute and the shallower breath just at the beginning of the following minute, the total ventilation of the first minute is increased at the expense of the second. Thus the total ventilation in a healthy subject for six successive minutes was as follows: 7·35, 6·65, 6·15, 8·60, 6·70, 6·35 litres. (Throughout this paper the figures for the ventilation indicate so many litres.) Consequently it is impossible to fix the particular minute after exercise when the total ventilation becomes exactly the same as that at rest. Even if it were possible, it would be necessary for many gassed patients to wear the valves for ten minutes or more after the end of the exercise; this is undesirable, as excessive salivation causes discomfort; the gassed patient is more sensitive than the normal subject to such discomfort, and his breathing is thus easily made irregular.

IV. *Dyspnoea Ratio.*

Instead of attempting to fix the time required for the ventilation to become normal, we estimated the amount by which the total ventilation during the second, third, fourth, and fifth minutes after exercise exceeded that during four

minutes at rest. This is conveniently expressed as a ratio R, where R = sum of the total ventilation of second, third, fourth, and fifth minutes after exercise ÷ 4 (total ventilation per minute at rest).

In choosing the period for the dyspnoea ratio we did not include the total ventilation during the first minute after exercise, for just at the end of an exercise the respiration is deep and rapid, and if the bag is not connected at exactly the right moment a deep breath may be missed or wrongly included, and thus considerable error introduced.

The dyspnoea ratio (column 7, Table I) varies somewhat from week to week in the same individual. Some variation is to be expected for two reasons.

(1) It is difficult to exclude completely *all* psychical influence in any investigation on respiration; the respiration is so readily altered by volition, that it is not easy for the subject always to obey the injunction to breathe 'absolutely naturally'.

(2) If a man does the same exercise in the same time on several occasions during a period of three months (the observations on H. C. extended over this period), it is certain that external conditions, such as weather, temperature, &c., and slight alterations in his physical condition,[1] will affect the degree of dyspnoea produced; for example, if a man runs 100 yards in exactly 12 seconds once a week for three months he will not feel equally breathless on each occasion.

The results given in Table I on H. C. require some analysis, as they illustrate an important point. Although the dyspnoea ratio varies 18 per cent., it is much more constant than the total ventilation during exercise or during the second, third, fourth, and fifth minutes after exercise; the variation in the former is 30 per cent. and in the latter 51 per cent. The dyspnoea ratio, in spite of its variation, is the nearest approach we have to a constant. The other exercise in Table I bear out this conclusion.

Of the examples of exercise 2 done by H. C., the last on the list illustrates the necessity of measuring the total ventilation before each exercise. If we had not done this, but had taken the average ventilation at rest for the previous exercises, i.e. 5·31, the value of the dyspnoea ratio would have been $\frac{67{\cdot}23}{21{\cdot}24}$ or 2·84. It will be noticed that H. C.'s ventilation at rest when this last exercise was done was 10·72, about twice the average of that found on previous occasions. We have no doubt that the higher figure was correct, and was not due to any experimental error. His ventilation at rest was estimated on several occasions about this period, and was always about 10 litres per minute. He was, moreover, quite accustomed to breathing with the valve, so there was no reason to suppose that the increase was due to any mental influence. We are at a loss to account for the high ventilation. The weather was hot at the time, but it is hardly likely that a rise in the external temperature was sufficient to double the ventilation.

[1] We have had a few observations on this point; if the subject was exercised on the morning after a sleepless night, at the end of a tiring day, or when he had a slight headache or cold (conditions which would affect his 'fitness'), the value of the dyspnoea ratio was higher than normal.

The total ventilation *during* exercise bears no constant ratio to that during rest; e. g. H. C. on the first occasion quoted in Table I, 2nd exercise, breathed 4·95 litres at rest, and 31·5, or roughly six times as much, during exercise, whilst on the last occasion he breathed 10·72 litres per minute at rest and 33·5, or only three times as much, during exercise. The effect of the exercise, is therefore, rather to add a definite amount to the ventilation at rest than to multiply it by a constant factor.

V. *Conditions affecting the Dyspnoea Ratio*

The exercises were all done at least an hour after a meal. Directly after a meal the dyspnoea ratio is irregular. The ratio is much higher than normal if the exercise is done directly after the subject rises in the morning; ratios of 1·91, 1·95, and 2·13, as compared with an average of 1·71, were obtained at this hour in the case of H. C. over exercise 2 on three successive mornings. In the case of G. H. H. the early morning values over the same exercise were also higher, viz. 1·71, 1·73, and 1·99, as compared with an average of 1·46.

TABLE II.

Exercise I.

Atmosphere. % CO_2.	Resting.	During.	1st Min.	Total.	Ratio.
G. H. H.					
1·15	5·96	21·80	15·52	25·70	1·08
2·4	8·32	36·70	24·95	42·15	1·27
2·7	10·01	35·30	24·15	45·17	1·12
H. C.					
1·15	7·39	23·55	14·40	37·07	1·15
1·15	7·74	27·15	16·25	35·80	1·16
2·1	7·66	28·50	15·75	37·40	1·22
,,	8·02	28·35	18·40	40·15	1·25
P. K.					
1·13	10·11	28·75	18·75	45·75	1·13
1·13	10·49	27·90	18·00	49·50	1·18
2·04	10·15	34·55	23·75	48·00	1·18

Exercise II.

G. H. H.					
1·15	6·51	38·85	27·37	37·35	1·37
,,	6·70	36·35	28·75	36·35	1·34
,,	7·81	30·95	33·70	49·10	1·57
,,	9·16	35·00	33·85	52·10	1·42
2·5	10·85	50·15	40·92	64·95	1·50
,,	11·12	47·70	44·00	67·89	1·52
H. C.					
1·10	6·05	30·80	27·15	45·67	1·88
,,	6·62	30·75	25·40	44·90	1·69
,,	6·73	32·30	29·00	45·67	1·82
2·1	8·12	35·58	31·70	54·95	1·69
,,	8·73	39·12	32·50	59·45	1·76
P. K.					
1·13	11·97	27·60	28·50	62·00	1·29
,,	11·64	33·70	30·60	65·65	1·41
2·04	11·17	37·25	33·70	67·55	1·49

Seeing that the dyspnoea ratio is dependent on the ventilation at rest, we increased the ventilation in three subjects by adding varying amounts of CO_2 to the inspired air. This was done by connecting the respiratory valve with a chamber of 9,000 litres capacity containing the required percentage of CO_2. The air in the chamber was kept mixed by an electric fan. Table II shows that under these conditions the total ventilation at rest is increased, while the dyspnoea ratio remains approximately the same as it was when the subject breathed air.

Having established the fact that the dyspnoea ratio is fairly constant for the same individual over the same exercise, we examined twelve healthy students of 18–25 years of age with the object of finding the normal limits of variation. We chose a series of exercises each lasting $1\frac{1}{2}$ minutes, but increasing in the amount of work done.

VI. *Results of Healthy Men*

The subjects fell into two classes, *A* and *B*; class *A* consisted of men who were taking vigorous exercise, such as football, rowing, &c., once or twice a week, and who considered themselves to be in good training; the men in class *B*, either because they were reading for examinations, or from disinclination, did not play games, and said they were in bad training. The men in class *C* both had healed wounds of the arm, but were otherwise fit and had been up and about for several weeks.

TABLE III.

Experiments on Normals.

		A. 290 ft. lb.	B. 3,800 ft. lb.	C. 5,600 ft. lb.	D. 7,020 ft. lb.	E. 8,740 ft. lb.	F. 10,330 ft. lb.
Group A	F. W. R.	1·09	1·17	1·27	1·37	1·58	1·63
	E. M. T.	1·16	1·28	1·33	1·46	1·59	1·77
	J. M. S.	1·11	0·88	1·23	1·32	1·46	1·54
	G. D. T.	1·07	0·91	1·20	1·25	1·36	1·55
	J. W. H.	0·97	1·06	1·15	1·31	1·42	1·74
	J. R.	1·01	1·08	1·24	1·38	1·69	1·78
	R. A. H.	1·07	1·10	1·19	1·31	1·57	1·71
	H. E. T.	1·09	1·05	1·39	1·40	1·67	1·93
Group B	S. W. G.	1·19	1·21	1·39	1·67	1·91	2·14
	A. S. H. W.	1·12	1·20	1·39	1·52	1·70	2·21
	J. H. S.	0·98	1·10	1·35	1·47	1·78	2·48
	F. D. H.	1·06	1·21	1·28	1·47	1·71	2·15
Group C	A. P.	0·90	0·97	1·14	1·41	1·62	2·17
	R. C.	1·07	1·19	1·26	1·37	1·74	1·90
Group A	Average (trained men)	1·07	1·07	1·23	1·34	1·52	1·67
Group B	Average (untrained)	1·09	1·18	1·35	1·53	1·77	2·24
Group C	Average	0·98	1·08	1·20	1·39	1·68	1·96

Two features are common to groups A and B.

(1) Over the first two exercises (both of which are very easy), the value of the dyspnoea ratio is approximately unity; this is an expression of the fact that one minute after the exercise is finished the subject's ventilation has returned to what it was before exercise.

(2) From the second exercise onwards the value of the dyspnoea ratio increases with an increase in the amount of work done.

We should expect this increase if the value of the dyspnoea ratio is a measure of the degree of dyspnoea, for the degree of dyspnoea will naturally be greater with a greater amount of work.

If group A alone is considered it is seen that the value of the dyspnoea ratio over any particular exercise does not vary very much among the different members of the group, except in one or two instances. It is fair to assume that in all trained men the degree of dyspnoea caused by a moderate amount of exercise will be about the same; this similarity among the trained men is expressed by the similarity in the value of the dyspnoea ratio.

If group A is compared with group B the figures show that over the easier exercises there is not much difference in the value of the dyspnoea ratio; over exercise *D*, however, *R*, the dyspnoea ratio, is slightly higher in group B, over exercise *E* the difference is more marked, and over exercise *F* it is considerable. The method thus distinguishes the trained from the untrained in terms of work; lack of training begins to be shown over exercise *D*, and is very obvious over exercise *F*.

The men in group C behave similarly to those in group B. They were examined for comparison with the 'gassed' patients (see Table V), as it was thought that possibly the high dyspnoea ratios of some of the 'gassed' patients over the exercises of moderate severity might simply be the result of the softening effect of a prolonged stay in hospital (Pte. P. had been in hospital a year and Pte. C. six months). A comparison of their dyspnoea ratios with those of the gassed patients shows that this was not the case.

Breathless Men.

A man judges of whether he is in good training or not largely by the amount of exercise which makes him 'out of breath', i.e. which gives him a definite amount of dyspnoea. If then we wish to equate a man's dyspnoea against the exercise which produces it, can we use the dyspnoea ratio as a test of the breathlessness? Or should we rather devote our attention to the total ventilation during and after exercise? Any factor used to measure dyspnoea must satisfy the following conditions:

(1) It must be reasonably constant for the same individual, due allowance being made for slight variations in physical fitness.

(2) It must be approximately the same for all individuals in approximately the same condition of physical fitness.

(3) It should, therefore, be capable of distinguishing trained from untrained men, and must distinguish all healthy men from men suffering severely from pathological conditions known to cause dyspnoea.

It has already been shown that the dyspnoea ratio satisfies the first and second conditions, whereas the total ventilation during the after exercise does not. The same is true of the third condition, as is shown in Table IV, in which the total ventilation during and after exercise in three normal men is compared with that of three patients, who, from one pathological cause or another, were short of breath. The patients have not a greater total ventilation during exercise than the normal men, and although on the cessation of exercise the difference is apparent in some cases, it is not so in all. The dyspnoea ratio, however, clearly distinguishes the normal from the abnormal in all three cases, and its value is particularly well shown in the case of Capt. R., who, after his exercise, was to the eye obviously much more out of breath than the control subject; his total ventilation during exercise was less than that of the control subject, and after exercise it was about the same, whereas there was a difference of nearly 100 per cent. in the dyspnoea ratio. We have examined a considerable number of men suffering from dyspnoea on exertion due to organic heart disease, 'D. A. H.', emphysema, and nephritis, and they all bear out the conclusion that the dyspnoea ratio affords the best test of dyspnoea, and that a man's capacity for work can be judged by finding the exercise over which his dyspnoea ratio is appreciably greater than normal.

TABLE IV.

Total Ventilation in Litres of three Pathological Cases (D. A. H., Mitral Stenosis, and Nephritis).

		Resting.	During Exercise.	1st Min. after Exercise.	Total 2, 3, 4, and 5 Mins.	Dyspnoea Ratio.
Case 1	Pte. T.	6·48	25·76	18·55	58·67	2·27
	Control	7·00	31·85	20·25	44·50	1·60
Case 2	H. F.	9·20	23·20	13·90	46·42	1·30
	Control	7·26	21·75	11·20	28·74	0·99
Case 3	Capt. R.	5·70	19·76	18·74	46·04	2·02
	Control	10·72	32·40	19·36	47·70	1·11

Case 1 was a severe case of D. A. H.
Case 2 was a mitral stenosis and auricular fibrillation—heart much enlarged.
Case 3 was a nephritis with anaemia (haemoglobin 66 per cent.).

Dyspnoea Ratio in Gassed Patients.

Having obtained a standard for healthy subjects we tested ten gassed patients by the same method. Table V shows the results. To take some examples; Pte. D. was a severe case of gas poisoning, and differed widely from the normal over the easiest exercise. Pte. J. was a very slight case of gas poisoning, and it was only when he reached exercise *E* that he showed

any difference from the trained men. Pte. S. was less severely affected than Pte. D., but became short of breath much more quickly than Pte. J.; Pte. S. begins to differ from the normal over exercise *C*.

The lower dyspnoea ratios (below 1·3) are not so reliable as the higher ones. If a man does no work his dyspnoea ratio should be unity, and it is clear that if some of the curves in Fig. 2 were continued they would not reach unity. The reason of this is that with a low dyspnoea ratio the breathing is much more affected by psychical influence, and with a high dyspnoea ratio the breathing is more automatic. Krogh and Lindhard (1) have shown that when a man is doing a constant amount of work per minute on the bicycle ergometer, his ventilation is at once increased if he is persuaded that there has been a sudden increase in the amount of work he is doing.

TABLE V.

Dyspnoea Ratios following Graduated Exercises.

Dyspnoea Ratio on Exercise / Patient.	*A*.	*B*.	*C*.	*D*.	*E*.	*F*.	Value of *E*.
Trained men	1·07	1·07	1·23	1·34	1·52	1·67	10,000
Pte. J.	1·14	—	1·20	1·37	1·84	2·28	7,970
Untrained men	1·09	1·18	1·35	1·53	1·77	2·24	7,750
Pte. McL.	1·19	1·24	1·44	1·57	1·91	—	7,340
Pte. G.	1·18	1·16	1·21	1·57	1·97	—	7,320
Pte. C.	1·18	1·37	1·52	1·95	2·50	—	6,000
Pte. B.	1·27	1·28	1·55	2·11	—	—	5,820
Pte. Gr.	1·27	1·28	1·60	1·90	—	—	5,780
Pte. S.	1·21	1·16	1·62	1·95	—	—	5,670
Pte. E.	1·19	1·33	1·64	2·07	—	—	5,600
Pte. D.	1·45	2·09	—	—	—	—	3,000
Pte. F.	1·46						
Lt. H.	—	2·43					

From the data in Table V we can estimate the efficiency of the patients. The practical test of their efficiency is the amount of work they can do for a given amount of exercise without breathlessness. This may be obtained at once from Fig. 2. The amount of breathlessness, i.e. the dyspnoea ratio, chosen as suitable is that experienced by a normal trained man as the result of an exercise of 10,000 foot-pounds in 1½ minutes. This is 1·64. We thus arrive at a figure *E*, which is a measurement in foot-pounds of the efficiency of the man, and is defined as the amount of work which he can do with the degree of dyspnoea which is experienced by a trained man doing 10,000 foot-pounds in 1½ minutes.

The values for *E* for the men shown in Fig. 2 are tabulated in the last column of Table V. The efficiency expressed as a percentage of that of the normal trained man is obtained by taking two noughts from the figure given there.

Description.	Value of *E* foot-pounds in 1½ minutes.	Percentage Efficiency.
Average trained man	10,000	100
Average untrained man	7,800	78
Pte. J.	8,000	80
Pte. Gr.	5,800	58
Pte. B.	5,800	58
Pte. D.	3,000	30

Pte. J. has a history of gas poisoning, and was suffering from lachrymation—the symptoms were so slight that they could all be ascribed to lack of training associated with a long stay in hospital.

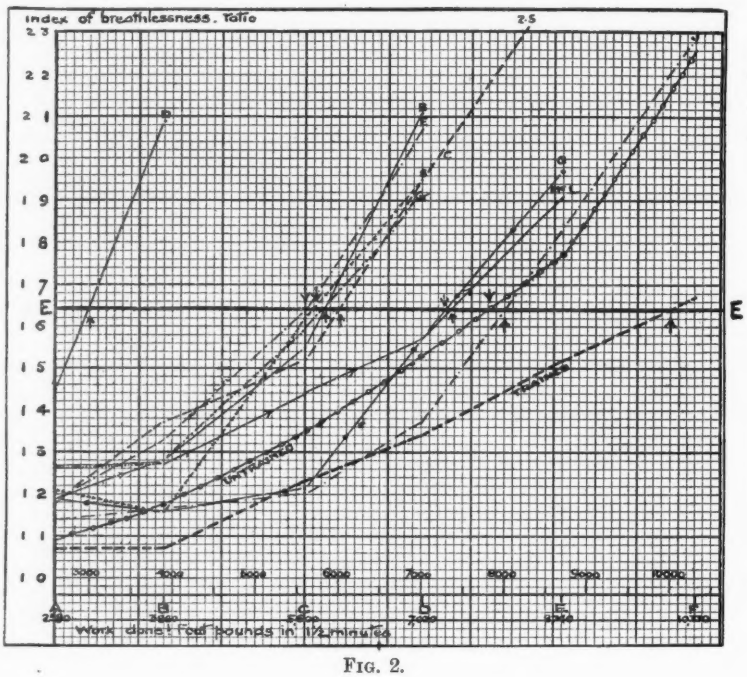

FIG. 2.

Depth of Respiration in Gassed Patients.

Our observations have given us the data for the calculation of the depth of respiration in a number of normal and gassed persons, though this calculation did not enter into our original thesis. In view of the importance of the subject, it seems desirable to tabulate the data which we possess. (See Table VI.)

TABLE VI.

Showing the Depth of Respiration of 'Gassed' Men during each Exercise of the Series. The figures give the depth in c.c.

During Patient.	Ex. *A.*	Ex. *B.*	Ex. *C.*	Ex. *D.*	Ex. *E.*	Ex. *F.*
Pte. F.	430					
Pte. G.	780	840	870	880	700	
Pte. S.	1,000	—	850	1,050		
Pte. McL.	740	920	1,130	1,140	1,230	
Pte. E.	840	690	860	880		
Pte. J.	780	730	800	980	1,060	1,230
Pte. Gr.	700	710	840	920		
Pte. D.	940	900				
Pte. C.	560	600	600	550	850	
Pte. B.	770	810	810	750		
Lt. H.	—	810				

The average depth of respiration in gassed men, both at rest and during exercise, is only slightly below that of healthy men ; indeed, in most cases, it falls within the normal limits (which it will be noted vary widely). This was generally the case even when the exercise given tried the patient nearly to the limit of his capacity (Table VII).

TABLE VII.

The Depth of Respiration of Healthy Men and 'Gassed' Men at Rest and during each Exercise of the Series. The figures give the depth in c.c.

	Healthy Men.		'Gassed' Men.	
	Average.	Range.	Average.	Range.
At rest	470	300–780	380	290–540
During exercise *A*	840	670–1,100	680	430–1,000
During exercise *B*	860	710–1,360	780	600–920
During exercise *C*	860	630–1,290	870	770–1,130
During exercise *D*	1,020	750–1,300	890	550–1,140
During exercise *E*	1,160	930–1,640	960	700–1,230
During exercise *F*	1,230	880–1,710	1,120 (one case only)	

We have observed only one case in which the depth of respiration was markedly shallower than normal during exercise. (See Pte. F., Table VI.)

In this particular case, Pte. F., the patient's depth of respiration during exercise (430 c.c.) was about half the average of that of normal subjects (840 c.c.), but only 37 per cent. below that of the *lowest* of the normals (670 c.c.). Pte. F.'s depth of respiration at rest (290 c.c.) was well below the average normal depth (470 c.c.), but only just below that of the lowest of the normals (300 c.c.).

Whilst it is clear that the respiration in the majority of the gassed cases is not shallower than that of many normal persons, we are not in a position to say that it is not somewhat shallower than before they are gassed, or to discuss the significance of a change within normal limits, if such exists.

Taking *E* (as is done in Table V) as the measure of the patient's efficiency we endeavoured to ascertain whether those persons who breathed most shallowly (*a*) at rest, (*b*) during exercise, were those who most easily became dyspnoeic. This we did both in the case of the normals and the gassed patients. The results are shown in Tables VIII and IX.

In Table VIII the first column of names is that of the patients given in the order of the depth of respiration at rest from the deepest to the most shallow. The second column of names is similar, but the order is that of the depth of respiration during exercise. In the last two columns the names and efficiencies represent the order of severity of the case. There is no sort of correspondence between these orders as given.

Table IX is constructed similarly to Table VIII, but has reference to healthy men. Here also the order of efficiency of the men does not seem to correspond with the depth of their respiration either at rest or during exercise.

Before concluding we must consider a possible criticism of the method employed. It may be urged that the actual wearing of the valve affects a man's

breathing to such an extent that no results on this method of experiment are reliable. It is true that a man often does breathe faster with the valve on, but this difficulty is normally overcome by getting him accustomed to it; one healthy man and four gassed men were rejected because their respiration rate was raised so much when the valve was put on.

TABLE VIII.

Showing Depth of Respiration in c.c. in 'Gassed' Men at Rest and during Exercise B compared with their Efficiency Figure E as given in Table V.

Patient.	Depth at Rest.	Patient.	Depth during Exercise *B*.	Patient.	Value of *E*.
Lt. H.	490	Pte. S.	? 925 (*a*)	Pte. J.	7,970
Pte. B.	440	Pte. McL.	920	Pte. McL.	7,340
Pte. Gr.	420	Pte. D.	900	Pte. G.	7,320
Pte. McL.	400	Pte. G.	840	Pte. C.	6,000
Pte. S.	400	Lt. H.	810	Pte. B.	5,820
Pte. J.	390	Pte. B.	810	Pte. Gr.	5,780
Pte. E.	350	Pte. J.	730	Pte. S.	5,670
Pte. G.	330	Pte. Gr.	710	Pte. E.	5,600
Pte. D.	330	Pte. E.	690	Pte. D.	3,000
Pte. C.	310	Pte. C.	600	Pte. F. }	less than 3,000
Pte. F.	290	Pte. F.	? 400 (*b*)	Lt. H. }	

(*a*) This figure is obtained by averaging the depth of respiration on exercises *A* and *C*.

(*b*) This figure is the depth on exercise *A*. Pte. *F.*'s depth of respiration was lower than that of any other patient over exercise *A*.

Pte. F. and Lt. H. did not do the series of exercises; their position on the list is inferred by comparison of their ratios with those of Pte. D.

TABLE IX.

Depth of Respiration in Healthy Subjects (1) *at Rest,* (2) *during Exercise F, and their Ratios over Exercise F.*

Name.	At Rest.	Name.	During Exercise.	Name.	Ratio.
	c.c.		c.c.		
J. W. H.	660	J. W. H.	1,710	J. M. S.	1·54
J. R.	530	J. R.	1,420	G. D. T.	1·55
R. H. H.	530	J. M. S.	1,380	F. W. R.	1·63
F. D. H.	510	J. H. S.	1,320	R. H. H.	1·71
J. M. S.	500	T. M. T.	1,280	J. W. H.	1·74
J. H. S.	500	H. W.	1,240	T. M. T.	1·77
T. M. T.	460	H. E. T.	1,120	J. R.	1·78
G. D. T.	440	G. D. T.	1,080	H. G. T.	1·93

As strong evidence in favour of the reliability of the method we adduce three facts:

(1) The results on trained men are very consistent.

(2) The method is sufficiently accurate to distinguish the trained from the untrained men very clearly.

(3) A classification of gassed men based on the exercise at which the ratio becomes definitely abnormal agrees closely with a classification based on other grounds.

We have not any data on patients whose ventilation at rest is much above the normal limits, and therefore cannot say whether the ratio would give a true idea of the degree of dyspnoea in such a case.

Summary and Conclusions.

1. Attempts have been made to measure the degree of dyspnoea of healthy and 'gassed' men and in a number of ways; for instance, by the rate of respiration, by the total ventilation, &c., under the conditions of rest, during exercise and after exercise.

2. The most reliable criterion to take is the total ventilation after exercise, but even the absolute measurement of this does not give a true index of dyspnoea; this is only to be obtained by taking the increment in total ventilation produced by the exercise. In concrete terms the best index we have obtained is the ratio of the total during the second, third, fourth, and fifth minutes after exercise to the total ventilation in the four minutes preceding exercise.

The exercises have lasted $1\frac{1}{2}$ minutes, and have been done on the bicycle ergometer.

3. By measuring this ratio over a number of graduated exercises we obtain a curve relating the degree of dyspnoea to the amount of exercise which produces it.

4. Taking as a standard a dyspnoea ratio of 1·64, which is that obtained in the average of trained men as the result of doing 10,000 foot-pounds work in $1\frac{1}{2}$ minutes, we can make a direct comparison between men of various conditions. The comparison consists in the actual amounts of work necessary to produce a dyspnoea ratio of 1·64. This quantity we call *E*, and take as the real index of the efficiency of the man as judged by his respiration.

This research was done under the direction of Mr. J. Barcroft, Assistant-Superintendent of Experiments, R.E., Experimental Station, Porton, and we are extremely indebted to him for much help and advice. We are indebted to the Medical Research Committee for considerable assistance in apparatus, &c.

REFERENCE.

1. Krogh and Lindhard, 'Regulation of Respiration', *Journ. Physiol.*, Camb., 1913-14, xlvii. 112.

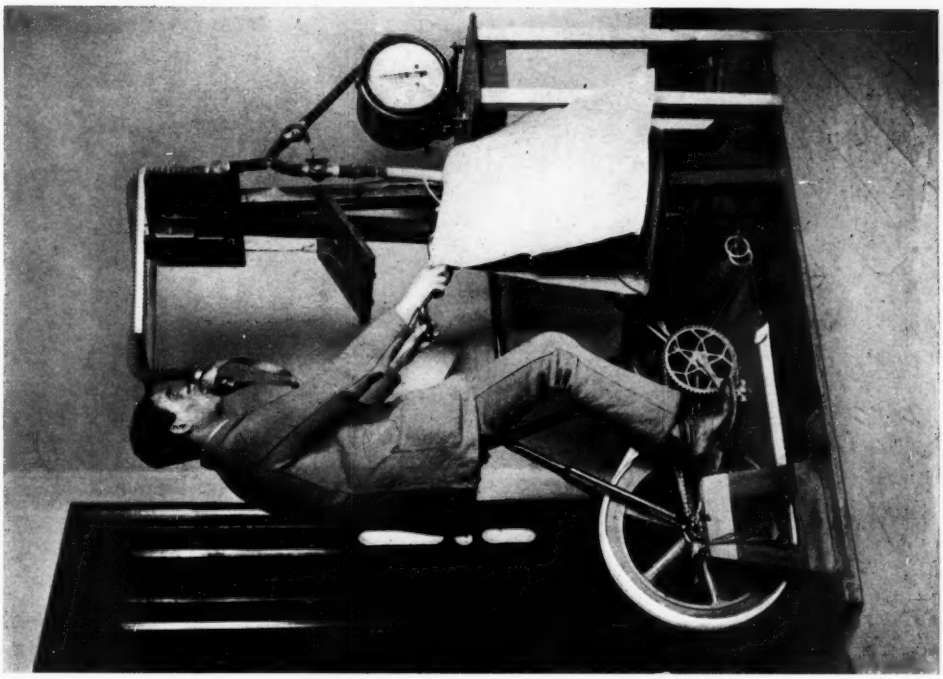

FIG. 1 B.

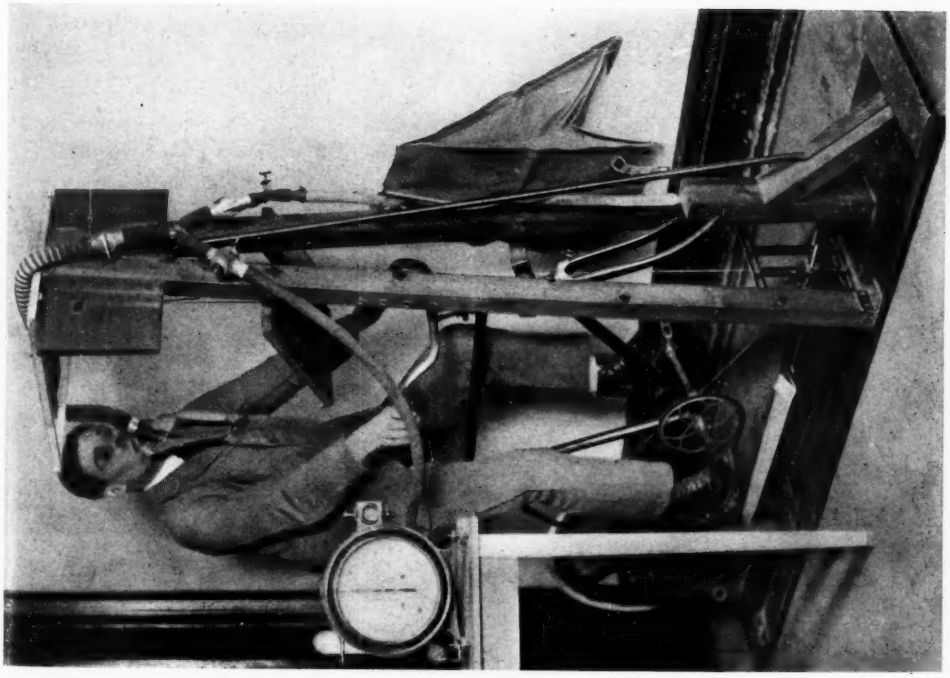

FIG. 1 A.

THE TREATMENT OF CHRONIC CASES OF GAS POISONING BY CONTINUOUS OXYGEN ADMINISTRATION IN CHAMBERS [1]

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Introduction.

The treatment of chronic gassed patients by the administration of oxygen was suggested by the possible interpretation of the symptoms they exhibit. The symptoms to which our attention was specially drawn were: (1) Disordered action of the heart. (2) Nocturnal dyspnoea. (3) High red blood counts (polycythaemia). (4) Low percentage of CO_2 in alveolar air. (5) Acidosis and kindred conditions.

A single case may not show all these symptoms to the same degree. Indeed, in the report by Hunt and Price Jones,[2] which drew attention to polycythaemia as an obvious feature of chronic cases, the cases which they observed were classified into: (1) those in which polycythaemia and nocturnal dyspnoea were conspicuous, and (2) those in which disordered action of the heart was most prominent. Between these extreme types there were intermediate cases showing symptoms common to each group.

Douglas (1) examined the alveolar air in a number of Hunt's and Price Jones's cases, and found an abnormally low CO_2 pressure in many of them—a research which is not quite simple of interpretation owing to uncertainty as to whether the alveolar air of gassed patients can be regarded as of uniform composition (2).

Sleeplessness, neurasthenia, and nocturnal dyspnoea have been described as leading symptoms of patients who had suffered from chronic gas poisoning in the filling factories, (3) associated often with breathlessness on exercise and disordered action of the heart.

Acidosis has been observed in gassed cases of the severer type at Boulogne (4) after the gas attacks in April, May, and June, 1915, and also in cases sent to the Military Hospital at Hampstead (5) for investigation. An exaggerated acidosis on exercise has also been observed in gassed animals (6).

The fundamental idea on which our treatment is based is that the whole

[1] The chambers consisted of three rooms, of capacity of 10, 10, and 12 cubic metres respectively, made of plate glass in iron frames and fitted with the necessary scrubbers for the removal of CO_2 and aqueous vapour.

[2] Hunt and Price Jones, Report forwarded to G.H.Q., France.

[Q. J. M., Jan., 1920.]

train of symptoms shown by these patients is the same as that exhibited at high altitudes. Among such the occurrence of sleeplessness, nocturnal attacks of breathlessness, and rapidity of the pulse after exercise is common, and polycythaemia is now beyond doubt (7). Acidosis, (8) especially in exercise, has been observed as a well-marked phenomenon as well as its complement lowered CO_2 pressure in the alveolar air. It is true that at high altitudes not all of these symptoms occur in an equal degree in every person, and in this there is a marked resemblance to the effect of gas poisoning.

As rarefied air, or, more precisely, insufficient available oxygen, is undoubtedly the cause of the trouble at high altitudes, it seemed reasonable to try the effect of a greater concentration of oxygen than these gassed patients were obtaining in ordinary air. Having obtained this suggestion, a method of treatment was worked out with rabbits at Cambridge. In these animals a chronic condition of polycythaemia was easily produced by exposure to chlorine or phosgene, and it was as easily abolished when the animals were placed in chambers containing 35–40 per cent. of oxygen (9). This result having been obtained, there seemed to be sufficient justification for the application of the same treatment to man.

The treatment consisted in keeping the patients in a chamber containing an atmosphere of 40–50 per cent. oxygen. The CO_2 and aqueous vapour were removed by passing the air over soda lime and calcium chloride. As a rule the patients remained in the chamber for sixteen out of the twenty-four hours for five days. They slept in the chamber every night, left the chamber after breakfast, and returned again just before tea.

The value of the treatment was judged by its effect on the patients' symptoms and partly by certain objective tests.

The tests used were the following: (1) A blood test; the degree of polycythaemia before and after treatment was determined. (2) A pulse test; the time taken for the pulse to return to the resting rate after exercise was determined before and after treatment.[3] (3) A respiration test; the degree of dyspnoea over a series of exercises was determined before and after treatment according to the method described in another paper in this number of the Journal (11).

If classified by the objective tests on which the patients were judged, they fall into two series:

Series I (Cases 1–14), judged principally on the fall of the pulse after exercise and on the reduction of polycythaemia.

Series II (Cases 15–25), judged on the improvement in their degree of dyspnoea after exercise.

The reason for the introduction of the respiratory test and the diminished emphasis on the pulse in Series II demands some explanation.

[3] In cases of effort syndrome, according to Gunson and Meakins ('The Pulse-rate after a Simple Test Exercise in Cases of Irritable Heart', *Heart*, Lond., 1917, vi. 285), the more rapidly the pulse returns after exercise to the rate at rest the greater the patient's capacity for muscular work.

The sign of polycythaemia only exists in certain types of patient 'gassed' with pulmonary irritants such as phosgene, and is seldom found in those gassed with dichlorethyl sulphide. After the autumn of 1917, therefore, polycythaemia was but rarely met with, and therefore our original programme of work would have thrown us entirely on the pulse as an objective sign. Our experience of the first dozen cases convinced us that, once we left generalities, there was no rule for the use of the pulse as a criterion which could be trusted implicitly. The test which we used in our earlier series was the extremely useful one suggested by Meakins, that of the time taken for the pulse to return to within six beats of the resting rate. In general this is a good rule; nevertheless we observed cases in which the pulse-rate showed great oscillations as the result of very moderate exercise. From being rapid it quickly became unduly slow.[4] Though, therefore, it soon came to within six beats of the resting rate and even dropped to twelve beats below it, the pulse could not be said to 'have settled down' to the resting rate in any sense. This condition of slow pulse was investigated to some extent and forms the subject of a separate paper in this series.

A further difficulty arises from the fact that in many patients the pulse does not fall steadily after exercise. A preliminary fall towards the end of the first minute or during the second may be succeeded by a subsequent rise lasting several minutes. If comparisons are to be made between different pulses, or the same pulse at different times, it should be specified whether the preliminary fall or the ultimate fall is the basis of the comparison.

Take the case of Case 10, Gunner A. The data are as follows:

Before Treatment.	Nov. 14, 1917. Pulse.	After Treatment.	Nov. 21, 1917. Pulse.
Before exercise	88	Before exercise	68
After exercise—		After exercise—	
1st ¼ minute	144	1st ¼ minute	116
2nd ,,	124	2nd ,,	84
3rd ,,	108	3rd ,,	80
4th ,,	96	4th ,,	80
2nd minute	96	5th ,,	68
3rd ,,	100	6th ,,	72
4th ,,	104	7th ,,	68
5th ,,	104	8th ,,	68
6th ,,	102		
7th ,,	100		
8th ,,	102		
9th ,,	98		
10th ,,	100		
17th ,,	96		
18th ,,	95		
22nd ,,	95		
23rd ,,	96		
24th ,,	96		

Taken on the data as given the verdict would be: 'Before exercise his pulse at rest was 88 and did not return to within six beats of this during 24 minutes' observation. After the treatment, his pulse at rest having been 68, it dropped to

[4] Case 2, Lt. P., affords a good example of this. His pulse-rate before exercise was 64; for eight successive quarter minutes after exercise it was 92, 80, 64, 60, 48, 52, 52, 48.

that figure in the fifth quarter minute after exercise'—a very satisfactory result if the statement be a fair one. It might be objected with some force that before the end of the first minute on Nov. 14 the pulse was to within eight beats of the resting value, that it might just as easily have been to within six, and in any case that two beats in quarter-minute counting is within the region of experimental error.

The interpretation of the rule is as follows: At the end of twenty-four minutes the pulse had not returned to within six beats of its pre-exercised rate before treatment; whilst after treatment it returned in the fifth quarter of a minute. Yet in the first instance, had the 88 before exercise been 89, and the first 96 been 95 (differences which are within the error of counting), the verdict would have been that the pulse before treatment returned in the fourth quarter-minute. Probably as correct an impression as any would be given by saying that the pulse before treatment returned in about 10 minutes, whilst after treatment it returned in 1¼ minutes. This form of words, however, violates all stated rules.

Indeed in the first series of figures, had the pulse dropped to 86 instead of 96 in the fourth quarter-minute and then proceeded as in the table, our view is that the figures would not indicate a better, but rather a worse cardiac condition than that which they actually show. After treatment the pulse returns to within eight beats of the resting rate at the beginning of the first minute; was the patient in a better condition before or after treatment? The particular effect of these observations, however, was to turn our attention to the discovery of an objective measure of dyspnoea.

The following is an account of the first series of cases:

Series I. Cases 1–14.

Histories of Cases. Case 1. T. D. The patient, aged 47, was a bricklayer's labourer by occupation. Previous to being gassed he was an exceptionally healthy man; he had not had any serious illness, and was able to do twelve to fourteen hours' heavy work a day without any feeling of fatigue. For the last eighteen months he had worked in a gas factory where chloropicrin was made. He had often been exposed to small quantities of gas, but not in sufficient quantities to cause any marked symptoms. On June 25, 1916, he was severely gassed; the immediate symptoms were dryness of the throat, nausea, vomiting cough, pain and tightness of the chest, and dyspnoea; he was not unconscious. Since that time he had suffered from headaches, muscular pain, and dyspnoea on exertion as well as 'asthma' at night. The asthmatic attacks usually began after he had been coughing; he had a feeling of suffocation, shortness of breath, and a 'heavy aching' over the front of the chest; he found that sitting up in bed or going to an open window afforded some relief. The attacks occurred every night, sometimes twice in one night, and might persist for as long as three hours; they seriously disturbed his rest, and he often did not sleep more than two hours a night. (These attacks seem to be typical of those described by Hunt and Price Jones.)

On examination he was a healthy-looking, rather thin, man. His pulse was 76, and of normal volume and tension. Occasionally a sibilant rhonchus, which disappeared on coughing, was heard in the chest, but otherwise the lungs appeared healthy. Nothing abnormal was found in the heart, nervous system, or

abdomen; the urine was normal. An X-ray examination of the chest made by Dr. Scales showed nothing obviously abnormal.

He was treated from July 24 to 28, 1917, with marked improvement. This improvement was maintained till August 9. Towards the end of August he became worse again. His relapse is to be ascribed to two causes: (1) between August 21 and 25 he did thirty-five hours' heavy work without any previous training and against advice; (2) on August 25 he was 'gassed' again. He was treated again from August 29 to November 1 and again improved. A month later a blood examination showed that the polycythaemia had not recurred. Unfortunately, it was not possible to repeat the exercise test, as he was not examined in the same place, and it was impossible to get an exercise that was comparable.

Case 2. T. J., aged 37. *Poisoning by Chloropicrin. History previous to being 'gassed'.* The patient had always been a healthy man, and accustomed to heavy work. For some years he was a bricklayer; in 1908 he became a traveller for a firm of drapers, and this involved walking several miles a day carrying samples weighing 50 lb. He entered a munition factory in April, 1916, and for three to four months did very heavy work without difficulty or shortness of breath. He used to play football regularly, but gave this up in 1912, as he had not time for it.

History of 'gassing'. From the beginning of August, 1916, the patient was often exposed to small doses of gas; on three occasions the symptoms were sufficient to necessitate rest in bed for two to three days, but on no single occasion were they at all alarming. The usual symptoms immediately after 'gassing' were cough, dyspnoea, pain all over the chest, vomiting, headache, and lachrymation. He was often giddy, but never unconscious.

Symptoms subsequent to being 'gassed'. The patient complained of the following symptoms:

(1) Pain in the throat and chest; this came on at any time of the day or night, and had no relation to exercise or to meals.

(2) Dyspnoea on exertion; he stated that he could walk half a mile in fifteen minutes, but that a faster pace caused discomfort.

(3) Dyspnoea at night; this came on in attacks, which were quite spasmodic in nature; he had a feeling of suffocation, and sat up in bed or walked about to get relief. The attacks lasted about an hour; they sometimes occurred for four or five nights in succession, but he might be free from them for three or four nights at a stretch.

(4) Cough; this was not severe, and he had only a little expectoration.

He was very subject to cold in the head.

Digestion was good.

Condition when examined on October 11, 1917. The patient was rather fat, but on the whole a very healthy-looking man. His tongue was clean, teeth fairly good; his palate was rather injected. Nothing abnormal was found on examination of the chest, abdomen, or nervous system. The urine was normal. His pulse-rate was 66; the artery was not thickened, and the pulse tension and volume were normal.

He was treated from October 11 to 17. As the result his pulse fell rather more quickly after the test exercise, for although the polycythaemia was diminished it was not abolished. He was therefore treated again from December 15 to 21. (In November he developed slight weakness of the left arm and leg, the result of cerebral thrombosis. The cause was not clear. The Wassermann reaction was negative, and there was no reason to suppose that 'gassing' was responsible for the thrombosis.) There was no improvement in his pulse-rate after the second treatment. The polycythaemia was further reduced.

Case 3. A., aged 31. *Poisoning by Chloropicrin. History previous to being 'gassed'.* The patient used to do very hard work in a colliery, and was

always able to do it without any difficulty. He enlisted in March, 1915, and was invalided out of the army in April, 1916, for a wound of the foot. Since that time he had done heavy work in a gas factory. He had always been a healthy man.

History of being 'gassed'. While he worked in the munition factory he was frequently exposed to small amounts of gas. About the middle of October, 1916, he stated he inhaled a large quantity, and had to remain in bed for three to four days. The immediate symptoms following this were headache, pain in the chest and abdomen, vomiting, dyspnoea, cough, and lachrymation; he was not unconscious.

Symptoms subject to being 'gassed'.

1. Pain over the left costal margin; this came on at any time of the day, and was not affected by exercise or by taking food.

2. Dyspnoea and giddiness on exertion; this prevented him doing heavy work for any long period.

3. Dyspnoea at night; these attacks were of the usual kind; they were associated with a feeling of suffocation and tightness in the throat; they lasted about half an hour, and occurred about once a week. He often sweated during an attack.

His digestion was good. He occasionally got headaches.

Condition when examined on October 11, 1917. The patient was a thin, but healthy-looking man. His teeth were fairly good, tongue clean. Nothing abnormal was found on examination of the chest, abdomen, or nervous system. The urine contained no albumin. The radial artery was not thickened, and the pulse was normal in volume and tension. He was treated from October 11 to 17.

Case 4. Sapper C., aged 31. This patient had been under the care of Lieut.-Colonel Drysdale (at St. Bartholomew's Hospital), who kindly furnished the following notes about him: 'Gassed, July 29. Mustard burn on the buttock. First symptoms: Choking, vomiting, partial loss of voice. Later: Conjunctivitis, headache, dyspnoea, pains in the stomach. Heart $4\frac{3}{4}$ inches from the mid-line in the 5th space. Red cells, 7 millions.'

Previous history. He was an electrician before joining the army. Except for occasional coughs and colds in the head, he had always been a very healthy man; he used to play football, and ran in races, and always had a very good 'wind'.

Symptoms subsequent to being 'gassed'.

1. Dyspnoea and precordial pain on slight exertion.

2. Attacks of dyspnoea at night. These attacks occurred once or twice a week, and lasted three to four hours. They were accompanied by headache, and a feeling of suffocation.

Condition when examined on October 21. The patient was a healthy-looking man. The heart's apex beat was just within the nipple line; the left border (by percussion) was $4\frac{1}{2}$ inches from the mid-line. Nothing abnormal was found in the lungs, abdomen, or nervous system; the urine was free from albumin.

He was treated from October 21 to 26 and again from November 1 to 4.

Case 5. Private D., aged 23. This patient had been at St. Bartholomew's Hospital under the care of Lieut.-Colonel Drysdale, who kindly sent the following notes about him: 'Gassed, June 21, by British trench mortar gas. Five minutes' exposure; box helmet worn. Helmet removed on "All clear". Immediate dyspnoea, headache, and nausea. Half an hour later severe pain in abdomen. June 23, cough began; June 24, vomiting. Abdominal tenderness. Heart $4\frac{1}{2}$ inches from mid-line in fifth space.'

Previous history. The patient was a bicycle maker before joining the army, and was accustomed to fairly heavy work. He used to play football, and was never troubled with shortness of breath. He stated that occasionally he had 'fainting attacks', but never consulted a doctor. (These attacks do not seem to have been epileptic.) Apart from this he was always a healthy man.

Present symptoms.

1. Dyspnoea and abdominal pain on exertion.
2. Occasional headache.

He slept well, and did not get any attacks of dyspnoea at night. His digestion was good.

Condition when examined on October 21. The patient was a healthy-looking man. The heart's apex was ½ inch internal to the nipple line; the left border (by percussion) was 4½ inches from the mid-line. Nothing abnormal was found in the lungs or nervous system. There was slight tenderness in the epigastrium; otherwise the abdomen was normal. The urine was free from albumin. He was treated from October 21 to 26, and again from Nov. 1 to 4.

Case 6. Pte. A., aged 20. This patient had been at St. Bartholomew's Hospital under the care of Lieut.-Colonel Drysdale, who kindly sent the following notes about him: 'Gassed', June 30, 1917. Phosgene (?). Helmet not in use. First symptoms: cough and choking, increasing dyspnoea, increasing pain in the chest, no lachrymation. Onset five minutes after exposure; vomiting one hour later, continuing for eight days. Heart's left border by percussion, 5 inches from mid-line in fifth space; some cyanosis. Red cell count 6·37 millions; leucocyte count 7,600; haemoglobin 93 per cent.

'Still suffers from dyspnoea, headache, and palpitation on slight exertion.'

Previous history. The patient was in the boot and shoe trade before joining the army; the work was quite light. He used to play football, and this did not cause him any abnormal dyspnoea.

Present symptoms.

1. Dyspnoea, headache, and precordial pain on exertion; he states that he could not walk more than a mile without considerable discomfort.
2. Dyspnoea at night. This came on in attacks, which were associated with headache and a feeling of suffocation. The attacks occurred every other night, and lasted a quarter to half an hour. His digestion was good.

Condition when examined on October 21. The patient was a thin, rather weakly-looking man. The left border of the heart by percussion was 5 inches from the mid-line in the fifth space. Nothing abnormal was found in the lungs, abdomen, or nervous system. The urine was free from albumin. He was treated from October 21 to 26.

Case 7. Sgt. S., aged 36. This patient was 'gassed' with chlorine on April 24, 1915, the first occasion on which gas was used by the Germans.

History previous to being 'gassed'. He had done heavy work all his life, and was a good athlete, having rowed and swam in races. He had had no serious illness.

Symptoms immediately after being 'gassed'. These were cough, dyspnoea, and pain across the chest; he did not vomit. He expected to recover in a day or two, but gradually got worse, and went to hospital on May 2.

Present symptoms.

1. Dyspnoea on exertion.
2. Headache, especially on waking up in the morning.
3. Constipation. His bowels were only open three times a week, although he took paraffin and often pills at night and salts in the morning.

His digestion was good. He used to get attacks at night, during which he

felt faint and had a sensation of tightness in the chest, but these attacks have now ceased.

Condition when examined on October 30. The patient was a spare, but very healthy-looking man. Nothing abnormal was found in the chest, abdomen, or nervous system; the urine was free from albumin. He was treated from October 31 to November 4.

Case 8. Pte. O'B., aged 22. This patient had been under the care of Lieut.-Colonel Drysdale at St. Bartholomew's Hospital.

Previous history. He had always been a very healthy man, and went in for various games and athletics; he had never been troubled with any shortness of breath.

History of being 'gassed'. He was 'gassed' on September 9, 1917. He felt dazed at first, and about five hours later the following symptoms began to appear: conjunctivitis, laryngitis, and cough; the first two disappeared after a few days, but he was kept in bed on account of 'chest trouble' for three weeks. He had no burns.

Present symptoms. He complained of dyspnoea and precordial pain on slight exertion. Sleep was often disturbed by cough, but he had no attacks of nocturnal dyspnoea.

Condition when examined, November 14. The patient was a healthy-looking man. He had a soft basal and apical systolic murmur, which was clearly 'functional', but beyond this nothing abnormal was found in the chest, abdomen, or nervous system. He was treated from November 14 to 18.

Case 9. Gnr. A., aged 19. *Mustard gas. Previous history.* The patient had always been a very healthy man, and was accustomed to take plenty of hard exercise; his 'wind' had always been good.

History of being 'gassed'. He was 'gassed' on September 28, 1917. He was not actually burnt, but his skin 'peeled'. He had conjunctivitis for some weeks. He also had much cough and expectoration.

Present symptoms. He complained of dyspnoea, thumping in the chest, and headache on exertion. He slept well and had no dyspnoea at night.

Condition when examined on November 14. The patient was a sparely-built, but healthy-looking man. He had a soft, localized, apical murmur, systolic in time and obviously only 'functional'; otherwise nothing abnormal was found in the chest, abdomen, or nervous system. He was treated from November 14 to 21.

Case 10. Cpl. H. H., aged 22. *Mustard gas.* This patient had been under the care of Lieut.-Colonel Drysdale at St. Bartholomew's Hospital.

Previous history. The patient was a grocer's assistant before enlisting. He did not do very heavy work, but was a fair athlete and able to cycle forty miles a day without any undue fatigue.

History of being 'gassed'. He was 'gassed' on August 1, 1917. He was burnt particularly on the arms, and also suffered from conjunctivitis, which was very resistant to treatment. He was kept in bed for eight weeks for 'chest trouble'. He stated that he became unconscious about eight hours after being 'gassed', and remembered nothing until he arrived in England about a fortnight later.

Present symptoms. He complained of pain in the chest and dyspnoea on exertion. For some weeks after being 'gassed' he suffered from headache, bnt this had now passed off. He slept well, and had no dyspnoea at night.

Condition when examined, November 14. He was a healthy-looking man. Nothing abnormal was found on examination of the chest, abdomen, or nervous

system. There was some opacity of the cornea of the left eye, and the conjunctiva was rather inflamed. There were some scars of burns on both arms. He was treated from November 14 to 19.

Case 11. Lt. P., aged 23. *History previous to being 'gassed'.* The patient was always a very healthy man, and used to play football and box. He did a fifteen-mile march in July, 1917, without any difficulty.

History of being 'gassed'. He was 'gassed' on September 11. He thinks the gas was phosgene. The first symptoms, which came on within ten minutes of being 'gassed', were vomiting, headache, pain right across the chest, cough, and dyspnoea. He also had slight lachrymation for two days, and some small boils on the neck, but no actual burns.

Present symptoms. He complained of dyspnoea on exertion and could only walk about 1½ miles at a stretch, and this took him ¾ hour. He also had spasmodic attacks of dyspnoea associated with giddiness during the day, but not at night.

Condition when examined on December 14. 'The patient was a healthy-looking man. Nothing abnormal was found on examination of the chest, abdomen, and nervous system. He was treated from December 14 to 21, and from February 6 to 11.

Case 12. Pte. F., aged 21. *History previous to being 'gassed'.* The patient was always a healthy man, but had never done heavy work or played games since his school-days. He used to bicycle, and could ride forty miles a day.

History of being 'gassed'. He was 'gassed' with phosgene in February, 1917, but returned to duty after three days. His immediate symptoms were vomiting, headache, cough, and dyspnoea. He never felt really well afterwards, always being 'short-winded'. He was 'gassed' again in July, but not sufficiently badly to make him report sick; from this time, however, his dyspnoea gradually became worse, and he went into hospital in October.

Present symptoms. He complained of dyspnoea on exertion, and of attacks of dyspnoea at night; these attacks occurred about once a fortnight, and lasted about half an hour.

Condition when examined on December 14. The patient looked well; nothing abnormal was found on examination of the chest, abdomen, or nervous system. He was treated from December 14 to 21, and from January 29 to February 3.

Case 13. Lt. R., aged 33. *Previous history.* The patient had been a healthy man on the whole, and was able to stand exertion very well. He had malaria in 1913; for some years he had been liable to bronchitis. He was 'gassed' in January, 1917, probably with phosgene. His immediate symptoms were headache, cough, and dyspnoea, but he did not think them sufficiently severe to report 'sick' at the time. About ten days later, however, he began to have attacks of 'asthma' at night (these attacks persisted for about ten months), and went to hospital.

Condition when examined on May 28. He complained of dyspnoea and precordial pain on exertion, and stated that this had not diminished at all for the last year.

On examination he was a very healthy-looking man. His pulse was regular, except for occasional extra-systoles, and of normal volume and tension. His heart was not enlarged and there were no murmurs. Nothing abnormal was found on examination of the other systems.

He was treated from May 5 to 10.

Case 14. Pte. H., aged 31. *Previous history.* He had always been a very healthy man and accustomed to heavy work.

History of being 'gassed'. He was 'gassed' with mustard gas on January 22,

1918. He suffered from conjunctivitis for a few days, and had some slight burns on the neck. He was kept in bed for a fortnight for 'chest trouble'.

Present symptoms. He complained of dyspnoea on exertion, and cough.

Condition when examined on March 10. He was a healthy-looking man. His pulse was regular and of normal volume and tension. His heart was not enlarged and there were no murmurs. Nothing abnormal was found on examination of the other systems.

He was treated from March 10 to 14.

TABLE I.

Time (Minutes) which elapses between End of Exercise and Return of Pulse to within Six Beats of Normal.[5]

	Before 1st treatment.	After 1st treatment.	Before 2nd treatment.	After 2nd treatment.	2–2½ months later.	Normal man doing same Exercise as Patient.	Control Exercise.*
T. D.	32	6	>21	1½	—	>21	
T. J.	1½	1	½	1	—	½	4 flights in 1′ 20″
A. A.	15	5	—	—	—	1	10 flights in 2′ 45″
Spr. C.	5	1	1	½	½	½	3 flights in 1′ 5″
Pte. D.	2	1	1	1	1	1	5 flights in 1′ 5″
Pte. A.	1	½	—	—	½	½	2 flights in 41″
Sgt. S.	10	1	—	—	2	1	6 flights in 1′ 40″
Pte. O'B.	5	1	—	—	½	½	3 flights in 1′ 15″
Gnr. A.	>21	1½	—	—	1½	1	4 flights in 1′ 20″
Cpl. H. H.	50	40	—	—	—	1	10 flights in 3′ 40″
Lt. P.	1	½	1	1	—	½	3 flights in 1′
Pte. F.	1	½	1	1	—	½	4 flights in 1′ 2″
Lt. R.	2	1½	—	—	—	½	5,650 ft. lb. in 1′
Pte. H.	did not fall in 6 minutes	1	—	—	—	½	6 in 2′

The figures indicate the number of minutes which elapsed after exercise before the pulse returned to within six beats of the rate at rest.

In the case of T. D. an easier test exercise was given when he was treated on the second occasion. The control subject's pulse returned to the resting rate in the sixth minute after the harder exercise, and in the first minute after the easier exercise.

* T. D. 12 flights of stairs in 4 min. (before and after first treatment).
4 flights of stairs in 1 min. 5 secs. (before and after second treatment).

Effects of treatment. Table I shows the effect of the test exercises on the return of pulse-rate before and after treatment. Lt. R. did an exercise on the bicycle ergometer. In all the other cases the exercise consisted in walking up and down one or more flights of stairs; the number of flights varied in different cases, but every patient kept to the same number of flights throughout, whether

[5] We have regarded ½ minute as the smallest useful interval to observe.

treated once or twice. The only exception to this was T. D.; his exercise on the occasion of his second treatment was easier than his original; he was unable to do the harder exercise again owing to the fact that he was 'gassed' a second time between his two treatments.

In the cases of Lt. P., Pte. A., and Pte. F. the exercises caused so much dyspnoea that it was not possible to use a severer test; the exercise given was not sufficient to cause the pulse to remain above the resting rate for more than a minute. This was unfortunate, for an improvement of half a minute in the time of the pulse return was the utmost that could be expected, and it is much easier to judge the effect of treatment when the patient's pulse returns to the resting rate two or more minutes more slowly than the control subject's.

In considering the effect of treatment on the pulse-rate we can divide fourteen patients into the following groups:

(1) Seven patients whose pulse-rates after treatment showed a great improvement, viz. T. D., A. A., Sgt. S., Spr. C., Pte. O'B., Gnr. A., and Pte. H.

(2) Four patients whose pulse-rates after exercise returned normally at the end of treatment, but improved only slightly, being only slightly abnormal before treatment, viz. Pte. D., Pte. A., Lt. P. (after first treatment), and Pte. F. (after first treatment).

(3) Three patients whose pulse-rates still returned more slowly than normal after treatment, but showed some slight improvement, viz. Cpl. H. H., Lt. R., and T. J. (after his first treatment).

TABLE II.

		Before 1st treatment.	After 1st treatment.	Before 2nd treatment.	After 2nd treatment.	2–2⅔ months later.
T. D.	Red cells	6·1 mil.	5·2 mil.	5·9 mil.	5·2 mil.	
	Haemoglobin	102 %	96 %	103 %	100 %	
T. J.	Red cells	7·9 mil.	6·2 mil.	7·0 mil.	5·8 mil.	
	Haemoglobin	111 %	106 %	112 %	109 %	
A. A.	Red cells	6·5 mil.	5·1 mil.	—	—	5·4 mil.
	Haemoglobin	94 %	88 %	—	—	90 %
Spr. C.	Red cells	6·5 mil.	5·0 mil.	5·7 mil.	5·2 mil.	6·2 mil.
	Haemoglobin	103 %	94 %	96 %	93 %	98 %
Pte. D.	Red cells	6·3 mil.	5·4 mil.	6·1 mil.	5·2 mil.	5·2 mil.
	Haemoglobin	105 %	97 %	104 %	100 %	102 %
Pte. A.	Red cells	6·0 mil.	5·1 mil.	—	—	5·7 mil.
	Haemoglobin	93 %	92 %			
Sgt. S.	Red cells	5·9 mil.	4·9 mil.	—	—	5·2 mil.
	Haemoglobin	104 %	97 %	—	—	99 %
Pte. O'B.	Red cells	4·8 mil.	4·9 mil.	—	—	5·3 mil.
	Haemoglobin	88 %	87 %	—	—	88 %
Gnr. A.	Red cells	6·3 mil.	5·3 mil.	—	—	6·2 mil.
	Haemoglobin	101 %	92 %	—	—	98 %
Cpl. H. H.	Red cells	5·6 mil.	5·1 mil.	—	—	5·4 mil.
	Haemoglobin	111 %	102 %	—	—	103 %
Lt. P.	Red cells	7·5 mil.	4·9 mil.	5·3 mil.	5·2 mil.	
	Haemoglobin	104 %	97 %	98 %	100 %	
Pte. F.	Red cells	6·5 mil.	4·6 mil.	4·8 mil.	5·4 mil.	
	Haemoglobin	96 %	98 %	94 %	102 %	
Lt. R.	Red cells	4·9 mil.	4·6 mil.			
	Haemoglobin	96 %	98 %			

The effect of treatment on the red cell count and haemoglobin is shown in Table II. Eleven patients had polycythaemia; in all except one (T. J.) the red

cell count became normal as the result of treatment; in the case of T. J. the red count fell to 5·8 millions after his second treatment. Pte. O'B. and Lt. R. had normal counts before and after treatment. In five (T. D., A. A., Pte. D., Sgt. S., Cpl. H. H.) patients the blood remained normal for 2–2½ months as the result of one or two treatments. Lt. P. had a normal count seven weeks after his first treatment, and Pte. F. had a normal count six weeks after his first treatment after relapsing for a time. In three patients (Pte. A., Gnr. A., and Spr. C.) the polycythaemia had returned 2–2½ months after treatment. In the case of T. J. the red cell count rose between his two treatments. We have no data as to its condition subsequent to his second treatment.

In all cases the treatment relieved the patients' symptoms. After treatment T. D. and A. A. declared themselves fit for any work, and all the other patients that their dyspnoea on exertion was diminished, and that they could walk farther and at a faster pace.

Six patients (T. D., T. J., A. A., Spr. C., Pte. A., and Pte. F.) suffered from attacks of dyspnoea at night. None of them had any attack while under treatment, and in three patients (T. J., A. A., and Pte. A.) the attacks seem to have been permanently abolished. T. D. was quite free from attacks for four weeks after treatment, but they recurred after he was 'gassed' again; until this accident his improvement in this respect was very striking, for his attacks had been so frequent and severe that he never had a good night's rest. Spr. C. had one attack after treatment, but it was only a slight one. Pte. F. affords the only instance in which the attacks recurred with the same frequency and severity.

Lt. P. was subject to attacks of dyspnoea, sometimes associated with faintness, which came on when he was resting during the day, but not at night. These attacks were much less frequent after treatment, but were not abolished completely.

The effect of treatment on the attacks of dyspnoea at night is summarized below.

Number of patients out of 14 suffering from attacks of dyspnoea at night	6
Number of patients suffering from attacks during treatment . . .	0
Number of patients permanently cured of attacks	3
Number of patients permanently benefited	2
Number of patients not permanently benefited	1

Series II. Cases 15–26.

The following is an account of the second series of cases:

Case 15. Lt. H., aged 27. The patient had always been healthy, and was a fair athlete. He was 'gassed' on October 31, 1917, with phosgene; he had no conjunctivitis nor burns. His immediate symptoms were dyspnoea, cough, pain in the chest, and headache. He was treated in hospital for a week and then returned to duty; after a week, however, he began to suffer from dyspnoea, precordial pain, and great fatigue on exertion; he also had attacks of dyspnoea at night which were associated with a feeling of faintness; these attacks lasted

about half an hour, and for a fortnight after his return to hospital occurred every night; they gradually passed off.

When seen on January 16 he complained of difficulty in taking a deep breath, dyspnoea and precordial pain on exertion, and 'nervousness'; he stated that he was nervous when talking to people, easily startled, and sometimes seized with fear when walking along the streets in the dark.

On examination he was a very healthy-looking man; he was obviously nervous in conversation, his respiration-rate was very irregular, and there was a fine tremor of the hands. His pulse was regular and of good volume and tension. His heart was normal in size, and there were no murmurs. Nothing abnormal was found on examination of the other systems.

He was treated from February 6 to 11.

Case 16. Pte. Fr., aged 21. The patient had always been a healthy man, but was not accustomed to very heavy work or vigorous exercise. He was 'gassed' with phosgene in July, 1917; his immediate symptoms were cough, pain in the chest, dyspnoea, and headache. When seen on January 29 he complained of dyspnoea and precordial pain on exertion; he slept well and had no attacks of dypsnoea at night.

On examination he was rather a poorly-built man, but looked fairly healthy otherwise. His pulse was of normal volume and tension, and regular in rhythm. His heart was not enlarged; there was a 'functional' murmur at the pulmonary area. Nothing abnormal was found on examining the other systems.

He was treated from February 6 to 11.

Case 17. Cadet H., aged 25. The patient had always been a very healthy man, and accustomed to hard exercise. He was 'gassed' on October 17, 1917, with mustard gas; he was burnt, but not severely, on the back and legs; he could not see for a week, and some conjunctivitis persisted for six weeks. He was kept in bed for two or three weeks with cough and 'chest trouble'.

When seen on April 4 he complained of dyspnoea and 'tightness in the chest' on exertion, but had no other symptoms.

On examination he was a very healthy-looking man. His pulse was regular, and of good value and tension. His heart was not enlarged, and there were no murmurs. Nothing abnormal was found on examination of the other systems.

He was treated from April 4 to 10.

Case 18. Pte. S., aged 29. He was a healthy man, and capable of hard exercise before being 'gassed'. He was 'gassed' on October 18, 1918, with mustard, and possibly with phosgene as well. He had conjunctivitis, and was blind for a fortnight. He was not burnt. He was kept in bed for 'chest trouble' for about six and a half weeks.

On admission to hospital he complained of slight hoarseness and dyspnoea on exertion. He was a fairly well developed man, but rather thin. Nothing abnormal was found on examination of the chest.

He was treated with oxygen from December 15 to 25.

Case 19. Pte. Gr., aged 33. He was a healthy man, and fond of athletics. He was 'gassed' with mustard gas on October 18, 1918. He had very severe conjunctivitis, and was kept in bed for broncho-pneumonia for seven weeks.

On admission he complained of soreness of the eyes and dyspnoea on exertion. He had slight conjunctivitis, which was cured after about three weeks. There was nothing abnormal about the chest.

He was treated with oxygen from January 8 to 16 (eight nights).

Case 20. Pte. D., aged 19. He was a clerk, and had never taken vigorous exercise. He was 'gassed' with mustard gas on August 19, 1918. He had

conjunctivitis for three weeks, but stated that he did not begin to cough until about a fortnight after he was 'gassed'. He was kept in bed for three and a half months because he had a persistently rapid pulse. He does not appear to have had broncho-pneumonia.

On admission he complained that slight exertion caused dyspnoea and exhaustion. He was a poorly-developed man. His pulse-rate taken in the morning before he got up was 100–110 on three successive mornings. There was slight but definite enlargement of the thyroid and a fine tremor of the fingers. Nothing abnormal was found in the chest. He was not of a nervous disposition, and the eyes were not prominent. It was thought that hyperthyroidism was, at any rate, partly responsible for his condition, and he certainly responded very quickly to treatment with opium, belladonna, and bromide, his pulse-rate falling in a few days to 70 and the tremor disappearing altogether.

He was treated from January 18 to 23.

Case 21. Pte. J., aged 24. He was a healthy man before being 'gassed', and played football. He was 'gassed' with mustard gas on September 24, 1918. He was burnt on the face and head, but only slightly, and had conjunctivitis. He does not appear to have had broncho-pneumonia.

He complained of soreness of the eyes and dyspnoea on exertion. He was a healthy-looking man. He had slight lachrymation, but no conjunctivitis. Nothing abnormal was found in the chest.

He was treated with oxygen from December 7 to 12.

Case 22. Pte. E., aged 22. He was a healthy man before he was 'gassed'. He was 'gassed' with mustard gas on October 10, 1918. He had slight conjunctivitis and broncho-pneumonia, for which he was kept in bed for six weeks.

On admission he complained of cough and dyspnoea. He was a fat, but otherwise healthy-looking man. His heart was normal in size, and there were no murmurs. He had slight bronchitis.

He was treated from December 7 to 12.

Case 23. Pte. C., aged 20. He had always been a healthy man, and was fond of boxing. He was 'gassed', probably with mustard gas, on November 4, 1918. He had slight conjunctivitis, but no burns. Chest symptoms seem to have been slight.

On admission he complained of giddiness and dyspnoea on exertion. He was a healthy-looking man. There were no abnormal signs in the chest.

He was treated with oxygen from January 8 to 16 (eight nights).

Case 24. Pte. B. J., aged 30. He was a healthy man before being 'gassed', and used to play football. He was 'gassed' on August 19, 1918, with mustard gas. He was slightly burned on the arms and legs, and had conjunctivitis for a fortnight. He was kept in bed for cough for five weeks.

On admission he complained of cough and dyspnoea on exertion. For two or three nights he got attacks of dyspnoea lasting about a quarter of an hour. Nothing abnormal was found in the chest. His red cell count was 6 millions with a haemoglobin of 194 per cent.

He was treated from November 25 to 30. After treatment his red cell count fell to 5·1 millions with a haemoglobin of 98 per cent.

Case 25. Pte. J. C., aged 25. He had always been a healthy man before being 'gassed', and was able to play football and do heavy work. He was 'gassed' on October 10, 1918. He was slightly burnt, and had conjunctivitis for twelve days. He was kept in bed for cough for three weeks. Nothing abnormal was found in the chest except occasionally very slight bronchitis. His red cell count was 5·8 millions with a haemoglobin of 104 per cent.

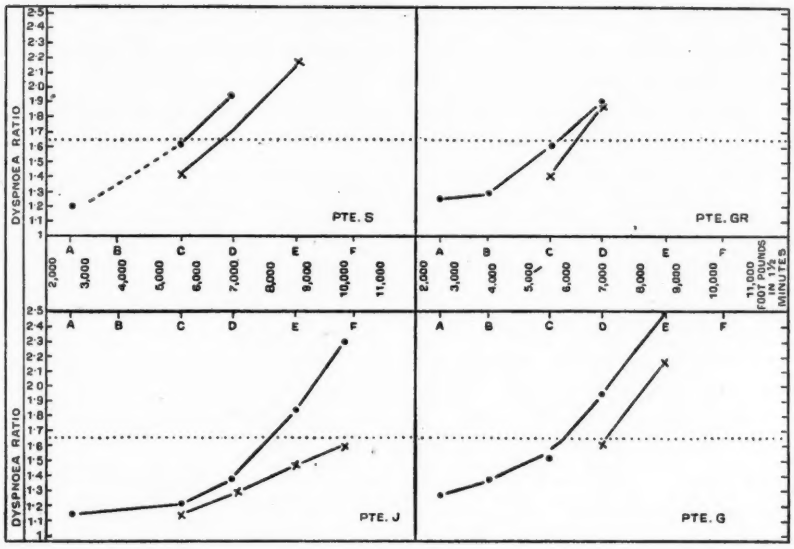

FIG. 1.

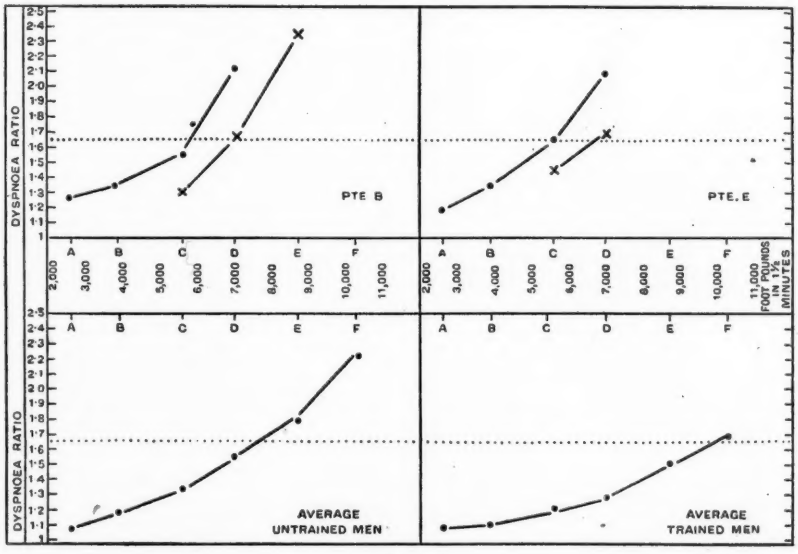
DYSPNOEA RATIO
PTE B
PTE. E
AVERAGE UNTRAINED MEN
AVERAGE TRAINED MEN
A B C D E F
2,000 3,000 4,000 5,000 6,000 7,000 8,000 9,000 10,000 11,000
FOOT POUNDS IN 1½ MINUTES

FIG. 2.

Figs. 1 and 2. •—•—•—• Curve before treatment.
×—×—×—× Curve after treatment.

He was treated from November 25 to 30. After treatment his red cell count fell to 5·3 millions with a haemoglobin of 99 per cent.

(The last two patients were treated in the oxygen chambers at Stoke, and were under the care of Dr. Sowry. We are indebted to him and Dr. Shufflebotham for permission to examine them before and after treatment, and to include them in this report.)

Case 26. Pte. B., aged 40. He was 'gassed' in April, 1918. He had slight conjunctivitis, but no burns. He was kept in bed for three weeks for 'chest trouble'. (It is uncertain what the gas was.)

On admission he complained of shortness of breath on exertion, but of no other symptoms. He was a healthy-looking man, and nothing abnormal was found in the chest.

He was treated from January 8 to 16 (eight nights).

Table III shows the 'Dyspnoea ratios' of the patients over a series of exercises before and after treatment.

TABLE III.

Showing the Ratios before and after Treatment over the Series of Exercises described in another paper in this number of the Journal.

Patient.	Exercise *	*A.*	*B.*	*C.*	*D.*	*E.*	*F.*
Pte. J.	Before	1·14	—	1·20	1·37	1·84	2·28
	After	1·00	—	1·13	1·30	1·49	1·56
Pte. S.	Before	1·21	1·16	1·62	1·95		
	After	—	—	1·43	1·72	2·12	
Pte. C.	Before	1·28	1·37	1·52	1·95	2·50	
	After	—	—	—	1·62	2·19	
Pte. Gr.	Before	1·27	1·28	1·60	1·90		
	After	—	—	1·46	1·89		
Pte. B.	Before	1·27	1·28	1·55	2·11		
	After	—	1·35	1·30	1·68	2·30	
Pte. E.	Before	1·19	1·33	1·64	2·07		
	After	1·18	1·36	1·48	1·70		
Pte. D.	Before	1·45	2·09				
	After	1·66	1·69				
Pte. Fr.	Before	1·44					
	After	1·03					
Lt. H.	Before	—	2·43				
	After	—	2·22				
Normal controls		1·07	1·07	1·23	1·34	1·52	1·67

Table showing the Ratios on Three Patients before and after Treatment who were tested with Exercises which were not in the Series above.

Patient.	Exercise.	Ratio before.	Ratio after.	Normal Ratio.
Cadet H.	4900 ft. lb. in 1½ minutes	1·34	1·25	1·15
Pte. J. C.	8 flights of stairs in 2 minutes	1·84	1·63	1·24
Pte. B. J.	6 flights of stairs in 2 minutes	2·30	1·98	1·24

* Exercises *A–F* each lasted 1½ minutes and were done on the bicycle ergometer. The amounts of work done were as follows:

Exercise	*A*	2590 ft. lb.
,,	*B*	3880 ,,
,,	*C*	5600 ,,
,,	*D*	7020 ,,
,,	*E*	8740 ,,
,,	*F*	10330 ,,

The degree of improvement is most easily visualized if the data in Table III are expressed graphically, the dyspnoea ratio forming the ordinate, and the work

which produced the breathlessness forming the abscissa. Such curves are given in Figs. 1 and 2. The graphic method possesses the additional advantage that the improvement in the man's condition may, by its aid, be determined and even expressed in absolute units.

When the average normal trained man does 10,000 foot-pounds of work in $1\frac{1}{2}$ minutes, he has a dyspnoea ratio of 1·64. This may be taken as the standard degree of breathlessness, and the question may be asked: How much work did the patients do (*a*) before treatment, and (*b*) after treatment, in order to produce the same degree of breathlessness as the normal man when he does 10,000 foot-pounds in $1\frac{1}{2}$ minutes? In Table IV these questions are answered, and further, the quantities of work obtained are given as a percentage of the normal, so that both an absolute and a relative measure of the man's efficiency is obtained. Lastly, from the above figures we can work out the degree of improvement in the man's condition; thus, in the case of Pte. B., when first tested, he could only do 5,800 foot-pounds for the same degree of breathlessness as the normal man experienced when doing 10,000. His efficiency was therefore 58 per cent. of the normal. On leaving the chamber his efficiency was 71 per cent. His improvement was therefore $\frac{71-58}{58} \times 100$, or 22 per cent. of his original efficiency.

TABLE IV.

	Pte. B.	Pte. E.	Pte. S.	Pte. Gr.	Pte. J.	Pte. C.	Normal Untrained.	Normal Trained.
Exercise (foot-pounds in $1\frac{1}{2}$ minutes) which produces a dyspnoea ratio of 1·65	5800	5600	5700	5700	8000	5900	7700	10000
Same after treatment	7100	6800	6700	6300	10200	7100		
Percentage efficiency before treatment	58	56	57	57	80	59	77	100
Percentage efficiency after treatment	71	68	67	63	102	71		
Improvement expressed as percentage of original condition	21	21	17	11	22	20		

The improvement in the cases may be considered from the point of view of (*a*) how much they improved, (*b*) how nearly they approximated to the condition of the normal untrained man at the end.

Of the six cases quoted in Table III, the figures given by Pte. D. are inconsistent and do not admit of interpretation. The others all show evidence of a greater or less degree of improvement. In the cases of Ptes. B., E., J., and C. this amounted to over 20 per cent. of the previous efficiency of the men. Ptes. Fr. and B. J. also improved considerably; Pte. S. improved 17 per cent.; Lt. H., Cadet H.,[6] and Pte. J. C. improved slightly. Pte. Gr. improved 11 per cent. only.

[6] On the assumption that the rise in the dyspnoea ratio varies with the square of the work, Cadet H.'s figures would give the following efficiencies: before treatment 69 per cent., after treatment 80 per cent., improvement 16 per cent. The assumption is sufficiently near to be taken as correct, but the individual figures are too uncertain to warrant interpolation.

As regards the final condition in which the men were left, taking 77 per cent. as the efficiency of the average untrained man, a glance at Table IV will show that three of the men (and probably also Cadet H.) had an efficiency of over 70 per cent. after their treatment, and were thus within a measureable distance of the normal.

Whilst the dyspnoea has been taken as the guide in the second series of cases, the pulse demands careful consideration (see Table V). The twelve patients under consideration, if divided according to the effect of treatment on their pulse-rates, fall under the following classification:

(1) Those whose pulse-rates at the conclusion of the treatment returned after exercise in the normal;

(*a*) Two patients who showed a considerable improvement, viz. Pte. S. and Cadet H.

(*b*) Five patients whose pulse-rates returned in the normal time at the end of treatment, but who improved but slightly, owing to the fact that their pulse-rates before treatment returned only slightly more slowly than in the control subjects, viz. Pte. E., Pte. J., Lt. H., Pte. Fr., and Pte. J. C.

TABLE V.

Time (Minutes) which elapses between End of Exercise and Return of Pulse to within Six Beats of Normal.

Patient.	Before Treatment.	After Treatment.	Control.	Exercise.
Pte. J.	1½	1	1	*F*
Pte. S.	3	1	1	*D*
Pte. C.	Did not return in 5 minutes	Did not return in 5 minutes	1	*E*
Pte. Gr.	4½	Did not return in 5 minntes	1	*D*
Pte. B.	2	2½	1	*D*
Pte. E.	1½	1	1	*D*
Pte. D.	Did not return in 5 minutes	Did not return in 5 minutes	½	*B*
Pte. Fr.	1	½	½	*A*
Lt. H.	2	Returned to within 8 beats of original rate in ½ minute, but did not fall below this	½	*B*
Cadet H.	Returned to within 7 beats of original rate in one minute, but did not fall below this	Returned to original rate in one minute	1	4700 ft. lb. on ergometer in 1½ minutes
Pte. J. C.	1	1	½	6 times up and down a flight of stairs in 2 minutes
Pte. B. J.	1½	1½	½	

(2) Four patients whose pulse-rates did not return in the normal time after treatment, and who made no improvement, and who therefore remained unsatisfactory throughout, viz. Pte. B., Pte. D., Pte. Gr., Pte. C., and Pte. B. J. It is clear that in Class 1 B the effect of treatment on the pulse could not be demonstrated on an exercise so small as the patients took; their improvement must therefore be judged by the more delicate test of dyspnoea.

As regards the effect of treatment on the patients' symptoms: with the

exception of Pte. Gr. and Pte. D. they all stated that they could stand a greater amount of exertion after treatment, and that exercise caused much less fatigue. Ptes. D. and Gr. felt no better, and their statement bears out the results of the test.

A legitimate criticism of the improvement wrought by oxygen treatment is that it is due to suggestion—to the psychological effect of the chamber, of blowing in the oxygen, &c.

We have watched this point closely and have failed to find any evidence in its favour. The following statements may be made on the subject:

(*a*) As regards polycythaemia, it is a type of condition which would be unlikely to be affected by suggestion.

(*b*) As regards tachycardia after exercise, we treated twelve cases of disordered action of the heart *not* following en gas poisoning. In these we could trace no certain improvement which was attributable to oxygen treatment. Yet there seems to be no reason why the pulse in the case of gas cases should yield to suggestion, whilst in other cases it should not.

(*c*) As regards nocturnal dyspnoea, which is more likely to be influenced by suggestion, the following experiment was made: A patient subject to nocturnal attacks was put in the chamber, and oxygen was blown in according to the usual method. A pipe, however, through which it could escape was left open, with the result that the percentage of oxygen in the chamber did not rise above 22. During the night an ample supply of atmospheric air was maintained. In the morning the percentage of oxygen was 20·5. This was done on three successive nights. On two occasions the patient woke up short of breath, and had to prop himself up in bed to obtain relief. He also said on the third morning that the treatment was doing him no good. Subsequently, he was treated with oxygen in the usual way; he had no further attacks, and said he was much improved.

N.B.—We have to record our thanks to the Medical Research Committee for much help given in the conduct of the above experiments.

Summary and Conclusions.

1. A description is given above of twenty-six cases of gas poisoning. They were treated by the continuous administration of oxygen. The patients were placed in chambers in which the percentage of oxygen aimed at, and usually maintained, was between 40 and 50. The usual term of residence was five days, sixteen or seventeen hours of each day being spent in the chambers. The night was always spent in them.

2. *Red cell count.* The effect upon the red cell count is as follows: if the red cell count is markedly higher than 5 millions, it is reduced by residence in oxygen, usually to just about that figure; if the red count, as is often the case, especially with mustard gas, is not raised above 5 millions, residence in oxygen does not alter it. The subsequent history of cases differs: in some the

red count tends to rise, in others it remains nearly normal at the end of 2½ months. As the red count fell, there was usually a fall—but a much slighter one—in the haemoglobin. The colour index therefore rose.

3. *Pulse.* An almost constant sign in the gassed cases which we have studied has been a failure on the part of the pulse to return normally after exercise to its resting rate. This condition has been benefited by the oxygen treatment in nearly all cases; and in about half it was brought to—or almost to—the normal condition.

4. *Nocturnal dyspnoea.* Of fourteen cases treated in Series I, six suffered from nocturnal attacks of dyspnoea. None of these had attacks in the chamber; three appeared to be permanently cured, and two others permanently benefited.

5. *Breathlessness on exercise.* No measurements were made in the first series of cases; the patients, however, all stated that they were able to walk faster and with less distress than before the treatment. In the second series of cases a definite test for dyspnoea was introduced, in which the opinion of the patients was not involved. Of the six cases thoroughly tested, four increased the quantity of work which they could do with a given degree of breathlessness by over 20 per cent., and two others by over 10 per cent.

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TABLE VI.

Case.	Status.	Gas.	Date of Gas.	Treatment.	Examination.	Red Cells.	Time for Pulse to return. Before Treatment.	After Treatment.	Control.	Nocturnal Attacks.	Abnormal Signs.
						millions.	mins.	mins.	mins.		
1. T. D.	Munition worker	Chloropicrin	June 25, 1916 Aug. 25, 1917	July 24–29, 1917 Oct. 29–Nov. 1, 1917	July 24, 1917 July 30, 1917 Oct. 29, 1917 Nov. 1, 1917 Nov. 29, 1917	6·1 5·0 5·9 5·2 4·5	32	6	—	Abolished till 2nd gassing, then improved	Polycythaemia: improved Pulse: improved Nocturnal attacks: improved
2. T. J.	,,	,,	Many slight gassings extending over 14 months	Oct. 11–17, 1917 Dec. 15–21, 1917	Oct. 11, 1917 Oct. 17, 1917 Dec. 15, 1917 Dec. 21, 1917 Jan. 23, 1917	7·9 6·4 7·0 5·8	1·5 — 1 — ½	— 1 — ½	½	Abolished permanently	Polycythaemia: improved Pulse: became normal Nocturnal attacks: abolished
3. A. A.	,,	,,	Oct., 1916	Oct. 11–17, 1917	Oct. 11, 1917 Oct. 17, 1917 Nov. 29, 1917	6·5 5·1 5·5	15 — —	— 5 —	1 — —	Abolished permanently	Polycythaemia: improved Pulse: improved Nocturnal attacks: cured *
4. C.	Sapper	Mustard	July 29, 1917	Oct. 21–26, 1917 Nov. 1–4, 1917	Oct. 21, 1917 Oct. 26, 1917 Oct. 31, 1917 Nov. 4, 1917 Jan. 23, 1918	6·5 5·0 5·7 5·0 6·1	5 — 1 — —	— 1 — ½ ½	— — ½ — —	Much improved	Polycythaemia: improved temporarily Pulse: became normal
5. D.	Private	Pulmonary irritant	June 21, 1917	Oct. 21–26, 1917 Nov. 1–4, 1917	Oct. 21, 1917 Oct. 26, 1917 Oct. 31, 1917 Nov. 4, 1917 Jan. 23, 1918	6·3 5·4 6·1 5·2 5·2	2 — 1 — —	— 1 — 1 1	1 — — — —	—	Polycythaemia: cured Pulse: became normal
6. A.	,,	Phosgene?	June 30, 1917	Oct. 21–26, 1917	Oct. 21, 1917 Nov. 26, 1917 Jan. 23, 1918	6·0 5·1 5·7	·1 — —	— ½ —	½ — —	Abolished permanently	Polycythaemia: temporarily improved Pulse: became normal Nocturnal attacks: abolished

* The words 'cured', 'abolished', &c., only apply to the period over which the cases were followed, given in the column headed 'Examination'.

TABLE VI (*continued*)

Case.	Status.	Gas.	Date of Gas.	Treatment.	Examination.	Red Cells.	Time for Pulse to return. Before Treatment.	Time for Pulse to return. After-Treatment.	Time for Pulse to return. Control.	Nocturnal Attacks.	Abnormal Signs.
						million.	mins.	mins.	mins.		
7. S.	Sergeant	Chlorine	April 24, 1915	Oct. 31–Nov. 4, 1917	Oct. 30, 1917	5·9	10	—	1	—	Pulse: became almost normal
					Nov. 4, 1917	4·9	—	1	—		
					Jan. 23, 1918	5·2	—	2	—		
8. O'B.	Private	? (No burns)	Sept. 9, 1917	Nov. 14–18, 1917	Nov. 14, 1917	4·8	5	—	½	—	Pulse: became normal
					Nov. 18, 1917	4·9	—	1	—		
					Jan. 23, 1918	5·3	—	½	—		
9. A.	Gunner	Mustard	Sept. 28, 1917	Nov. 14–21, 1917	Nov. 14, 1917	6·3	24	—	1	—	Polycythaemia: temporarily improved
					Nov. 21, 1917	5·3	—	1½	—		
					Jan. 23, 1918	6·2	—	1½	—		Pulse: became almost normal
10. H.H.	Corporal	,,	Aug. 1, 1917	Nov. 14–19, 1917	Nov. 14, 1917	5·6	50	—	1	—	Pulse: not much improvement
					Nov. 19, 1917	5·1	—	40	—		
					Jan. 23, 1918	5·4	—	—	—		
11. P.	Lieutenant	Phosgene?	Sept. 11, 1917	Dec. 14–21, 1917	Dec. 14, 1917	7·5	1	—	½	—	Polycythaemia: cured
					Dec. 21, 1917	4·9	—	½	—		
				Feb. 6–11, 1918	Feb. 6, 1918	5·2	1	—	½		Pulse (slight): not normal
					Feb. 11, 1918	5·4	—	1	—		
12. F.	Private	,,	Feb. 7, 1917 July, 1917	Dec. 14–21, 1917	Dec. 14, 1917	6·6	1	—	½	Not improved	Polycythaemia: cured
					Dec. 21, 1917	4·6	—	½	—		
				Jan. 29–Feb. 3, 1918	Jan. 29, 1918	4·8	1	—	—		Pulse (slight): not normal
					Feb. 3, 1918	5·4	—	1	—		Nocturnal attacks: not improved
13. R.	Lieutenant	,,	Jan., 1917	May 5–10, 1918	May 5, 1918	4·6	2	—	½	—	Pulse: slightly improved
					May 10, 1918	4·6	—	1½	—		
14. H.	Private	Mustard	Jan. 22, 1918	Mar. 10–14, 1918	Mar. 10, 1918	—	76	—	½	—	Pulse: became almost normal
					Mar. 14, 1918	—	—	1			
15–26.	See Tables IV and V										

MUSTARD GAS POISONING[1]

By C. M. WILSON and J. M. MACKINTOSH

A certain air of mystery has, from the first, gathered around the subject of poison gas.

The obligation of secrecy put upon all workers in this field, then and since, has ended in a very general failure on the part of the profession to grasp the true significance of a weapon new in warfare. The use of mustard gas by the enemy in 1917 and 1918 was in itself a bid for a decision on the great scale; it came to play on land the part the submarine filled upon the seas. And now that this ban has been removed, or at least partially removed, we wish, without further delay, to describe some of the clinical aspects of the larger campaign by which the initial success of the enemy—and it was no inconsiderable success—was happily converted into ultimate failure.

Already M. Achard (1), in the course of a recent communication to the French Academy of Medicine, has taken full advantage of his release, and his paper is an important contribution to the literature of gassing. He had a tale to tell of work of scientific value that was carried through in silence in the public interest, work of which it is high time that we should hear more, for, as M. Achard pleads, the sequelae of gassing will persist for some years, and their treatment can no longer be confined to army hospitals. He asks for a wider appreciation of these results, and seeks to awaken the curiosity of those who are not as yet familiar with their nature. 'Il importe donc que tout medécine les connaisse.'

Nevertheless, M. Achard was apparently unable to free himself of doubts; he could not forget that he was dealing, as we hope, with a subject the interest of which is now mainly historical, and accordingly he has limited the range of his discussion to the narrow boundaries of after-effects.

We may as well confess at the outset that we have not been content to limit the scope of this paper to such facts as may help in the after-treatment of pensioners, but have rather sought to rescue, while they are yet available, data which may presently enable the full story to be told. In this purpose we have been fortified not only by knowledge of the gross total of casualties, which in itself ensures for mustard gas a place apart in the history of the war, but also by the singular poverty of the official records that was brought to light in the course of our investigations.

The purpose of this paper is to analyse a consecutive series of 1,500 mustard gas casualties admitted to No. 7 Stationary Hospital between January 1 and

[1] 'Mustard gas'—dichlorethyl sulphide.

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October 31, 1918. We hope, by a careful examination of a number of casualties that is sufficiently large to justify broad conclusions, to determine the exact place of the various functional and organic results of mustard gas poisoning in the history of the subject, the proper relation of the part to the whole, so we may know, not what may happen after gassing, but what did happen, and in what proportion of cases it so happened. Reference is made throughout the paper to twenty-four necropsies made by Capt. Ingram on fatal cases and to sections of tissues taken from these fatal cases.

Table I shows the proportion of mustard gas casualties to the total gas admissions during a period of four months. The table is divided for purposes of comparison into two groups:

(1) The May to July group.

(2) The August group. This division is interesting in point of time, as the first group coincides with the German offensive, and the second with our counter-offensive.

TABLE I.

Gas Cases of All Kinds admitted May–August (inclusive), 1918.

	May–July		August.		Total.	
		%		%		%
1 'Mustard' gas	254	77	438	77	692	77
2 'Blue Cross'	35	11	50	10	85	10
3 'Phosgene'	17	5	34	6	51	6
4 'Lachrymatory'	13	4	25	4	38	4
5 'Not defined,' British, &c.	9	3	19	3	28	3
Total admissions	328	100	566	100	894	100

The table brings out two points: firstly, that the relative proportions of the various varieties of gas used by the Germans did not materially alter during the four months; and secondly, that the great majority (77 per cent.) of cases admitted were due to poisoning by mustard gas.

PART I.

FUNCTIONAL NERVOUS DISEASE ASSOCIATED WITH MUSTARD GAS POISONING.

Frequency.

The incidence of the commoner functional manifestations in this series of 1,500 mustard casualties is shown in Table II.

TABLE II.

Functional Disorder.	Total Number of Cases.	Percentages.
Functional photophobia	189	12·6
Functional aphonia	108	7·2
Functional vomiting	16	1
D. A. H.[2]	19	1·2

[2] Reference will be made under 'Effort Syndrome' to the inclusion of D. A. H. in the section dealing with functional-nervous disease.

Taken in conjunction with other and rarer functional disturbances, to be described later, it was estimated that a functional neurosis was recognized in 22 per cent. of all admissions in the mustard group, either on admission to No. 7 Stationary Hospital or within the period between admission and discharge from that hospital. This figure, however, is an understatement of the case. The examples of functional nervous derangements recorded in Table II are drawn from cases who, in the main, were subsequently transferred to convalescent camps. True, the incidence of these disorders is much commoner in mustard casualties of a mild type than in seriously gassed men, as shell-shock is relatively rare among the wounded, yet we know from following the after-history of men evacuated to England that not a few developed later the same neuroses.

We have to add to this source of error the inevitable tendency to group cases, functional in origin, under an organic heading. Bearing in mind the overwhelming preponderance of mustard casualties among gassed men, the significance of such a conclusion—that nearly a quarter of all mustard casualties exhibit a functional nervous disorder, which reacts promptly to suitable treatment—will be apparent, at least to those who are aware of the total number gassed after July, 1917. Yet those figures are not reflected in the literature. Now it is, perhaps, not altogether a matter for surprise that in the authorized versions—French, German, and English—no reference is made to functional phenomena, the pen in war being such an official instrument. It is more remarkable that the actual state of affairs had failed to impress those who worked in gas wards. That aphonia, blepharospasm, vomiting, occurred as functional sequelae of gassing was known; what was apparently not known was that these functional sequelae, so far from being exceptional and of little practical significance, were common and of primary importance. For the secret of the efficient control of wastage among gassed casualties lay in their recognition and treatment, and that wastage became at one time a military problem of the first order.

There were contributing causes which go far to explain the partial recognition of the functional element. Mustard admissions came in waves with a rush of wounded, and the consequent hungry demand for anaesthetists fell in such an emergency largely upon the medical division: there was an insistent call for beds, leading to the evacuation to England of doubtful cases, and, in the press and hurry of the time, systematic investigation became difficult. In brief, medical officers confronted by aphonia and vomiting perhaps too readily assumed that the trouble was organic. And while the failure to discriminate between an organic lesion and a neurosis implanted upon it resulted in wastage on a scale that caused the military authorities considerable anxiety, it so happened that in the literature a singular silence had fallen upon the one point which, from the practical point of maintaining armies in the field, most needed stressing.

The Rôle played by Functional Disorders in prolonging Invalidism.

We have, accordingly, to distinguish between the legitimate period of invalidism and that other very different figure which is the outcome of imperfect recognition of the functional element in gassed cases. And it follows from the considerations already set forth that in this we shall receive very little assistance from statistics collected from many hospitals. Unless a systematic attempt was made at the time to separate the functional element from the organic, it is idle to try to draw from notes written by different medical officers any conclusions as to the incidence of functional disorders. That they were not recorded does not necessarily mean that they were not present.

How far they were responsible for the detention in hospital of the patient must be determined by an examination of the results of a single unit where these factors were constantly borne in mind, and where one uniform method of investigation and detection was followed. These figures may be checked by a comparison (1) of the average stay in such a hospital of patients who were eventually returned to duty through a convalescent camp, (2) of the percentage of total mustard admissions evacuated to England, with the corresponding figures shown by different bases and by different hospitals at one and the same base. In the period May–August, 1918, 518 mustard cases were transferred from No. 7 Stationary Hospital to convalescent camps: only 174 within 14 days of gassing. The remaining 344 were classed for convenience as delayed cases, 14 days in hospital being taken as a working figure. In 42 of the 344 (12 per cent.) functional photophobia was noted, and of these 24 were delayed on that account alone, while in 67 (19 per cent.) functional aphonia was present as a cause of delay, and 40 were delayed on that account alone. Yet this is preventable wastage occurring in a hospital where the medical officers had special experience in gas, and where exceptional pains were taken to eliminate by early treatment the functional element with a view to transfer to convalescent camps. It is, perhaps, a reasonable inference that under less favourable conditions this preventable wastage grew. As a matter of fact, we know from figures, which it is not possible to print at the present time, that it grew in a very remarkable manner. These functional disorders were not legitimate reasons for delay in hospital. Facilities existed at convalescent camps for out-patient treatment, and we know that functional aphonia, photophobia, and vomiting react readily to early treatment.

These considerations require to be brought before those who have to deal with the assessment of gas pensions. It is already—and very rightly—the practice, especially where the clinical notes are poor or not available, to lay stress on the number of days or weeks a man spent in hospital as some rough measure of the severity of the initial lesion. This is only valuable if checked by knowledge of the various reasons that led to retention, some valid and some but the fruit of war conditions.

But the whole question is of interest from more than one point of view. In the study of functional nervous disease in war there is here a vast field that has lain fallow, while from the historical point of view essential data can still be gathered, without which it would be impossible to weigh accurately the military value of gas as an offensive weapon: not only its effects of wastage, but its effect on morale.

The medical historian has other duties. He, too, is concerned in the preservation of morale and in the control of wastage from the moment a man leaves his unit in the trenches till his return to a military depôt as a fit soldier. But he will also recognize that he has here a fair criterion of the efficiency of the medical arrangements of a modern army. He will note that both tests in their severest form were applied to the R.A.M.C. in France in gas poisoning. It is not our present purpose to anticipate his verdict.

Mode of Origin.

Reynell (2) has defined functional vomiting as 'the perpetuation by suggestion of a symptom, due, in the first place, to a pathological condition, such as that caused by gassing, dysentery, phthisis, or appendicitis'.

The initial acute gastritis, accompanied by frequent vomiting, set up by swallowing saliva containing mustard gas in solution, generally subsides within a few days, but 'in the predisposed neuropath, or in a soldier whose susceptibility has become exaggerated as a result of war strain, the vomiting may persist as an hysterical symptom after the organic disturbance which gave rise to it has disappeared'. An exactly similar explanation can be put forward for functional aphonia and blepharospasm.

In our earlier work we recognized two groups of functional photophobia:

(1) Arising out of a severe conjunctivitis which had cleared up.

(2) As a condition functional from the outset.

Photophobia, associated with severe eye lesions, was present in 352 cases of our series, and in a certain proportion it persisted as a functional condition after the organic trouble had subsided. But, apart from this group, in thirty-nine patients a marked blepharospasm, out of all proportion to the ocular signs, which were slight or absent, was noted from the outset.

This distinction is obviously applicable to the various other functional disorders following mustard gas; but it is clearly difficult, or impossible, to exclude the presence of a slight initial organic lesion. Nevertheless, with this difficulty in view, it appeared not improbable that emotion associated with a gas attack was the sole exciting cause of some of the examples of vomiting, photophobia, and aphonia in our series. This conception of a fraction of these functional disorders as purely emotional in origin and independent of organic damage is useful if it leads to a reconsideration of the meaning of these functional manifestations.

Significance of Functional Disorders following Mustard Gas.

Gas, after July, 1917, partly usurped the rôle of high explosive shell in bringing to a head a natural unfitness for war or less frequently a fitness sapped by exceptional stress of experience in the field. In many cases where the signs of gassing cleared up in a few days, we had to deal with a condition of mild gas shock, comparable to the slighter cases of shell shock which reach a Casualty Clearing Station after an action. This condition, with its accompanying functional nervous disorders, was an expression of trench fatigue.

To overlook this aspect of gassing was to invite loss of morale among gassed casualties on a considerable scale. It was necessary, indeed, to impress upon medical officers that these men were sent out from hospital not as semi-malingerers to be promptly returned to duty, but rather as examples of gas shock, who were transferred to convalescent camps for further treatment in more healthy surroundings, and in an atmosphere more calculated to restore morale. The organic lesions were negligible or absent—it was the mind that had suffered hurt.

Those who had been battalion medical officers were quick to see that it was not much use returning a man to the trenches unless he was sent back in good fighting trim. From this angle they were ready to co-operate in preventing that 'hospitalization' to which such men are peculiarly liable. From our early note-books, written before we were sufficiently impressed with these possibilities, the following notes on a case of functional photophobia are taken:

'The man is unwilling to take any interest in the ordinary daily life of the ward. Depressed and irritable, he is very loath to part with his eye-shade, and, when it was taken away from him, he twice contrived to reappear in it. Half the day he spends curled up on his bed, with head concealed in his pillow, more miserable than he had been in the acute phase of broncho-pneumonia and burns; when roused he shuffles slowly to his feet and blinks at his medical officer. He does not complain, but under questioning speaks of persistent irritation and watering of the eyes, though examination reveals nothing.'

Of all functional disorders photophobia appeared to be the most distressing to the victim, and, if allowed to persist, often completely demoralized him. It is not remarkable that neurasthenia was a common sequel of prolonged functional photophobia, which had escaped detection and treatment, and that we read of cases where this condition is advanced six months after gassing as the sole reason of detention.

These considerations are of some importance in the assessment of gas pensions. We do not exhaust the means of investigation in gassed men when we fail to find signs of organic disease in the chest. It would be as reasonable to dismiss a shell-shock applicant on the ground that his heart was normal.

We may add in passing that some of the ritual employed in searching for an objective test of dyspnoea in these men seems only too likely to perpetuate a condition which it is intended to relieve, as elaborate dieting, rectal feeding, &c., are the worst possible régime for cases of hysterical vomiting.

The less common Functional Manifestations following Mustard Gas Poisoning.

Functional analgesias, sometimes accompanied by subjective phenomena, were well-recognized sequelae of Blue X poisoning. They were rarer events after both mustard and phosgene poisoning, but they occurred. In one case there was a complete hemi-analgesia, and in another an extensive area of analgesia which cleared up with the use of the battery. Hysterical paralyses were rare. In a man with severe burns, corneal ulcers, and high fever complete functional aphonia was associated with hysterical paralysis of the legs, accompanied by kataclonic movements of the arms. In two other examples of loss of power of the arms the battery brought about a rapid restoration of function. These functional disorders of sensation and power were more common among gassed casualties than among wounded men, but they were rare events. They reacted readily to the measures employed in functional aphonia and the commoner disorders.

On the other hand, though such analgesias and paralyses are not confined to Blue X casualties, as is generally held, it is not difficult to include a Blue X case in the mustard group.

Case I. Private M. was admitted on the third day after gassing with a functional aphonia and photophobia, the picture at first resembling a mild case of mustard poisoning. But the gassing was followed immediately, without any latent period, by typical Blue X symptoms. Inquiry as to the gas used on that date on the particular sector his unit occupied, and into the nature of the casualties from that area admitted to other hospitals, together with the examination of other men of his unit, gassed at the same time and place, and admitted to No. 7 Stationary Hospital, made it clear that Blue X was the only gas employed. In this man there was marked analgesia over extensive areas of both legs. But when every allowance is made for possible errors of this nature, the matter was clinched by the appearance of such disorders in cases with burns and corneal ulcers where there was apparently no question of a mixed gas bombardment.

Hysterical analgesia and paralysis are rare in mustard poisoning, but they do occur. They are found in men gassed by mustard gas, by phosgene, or by Blue X, in wounded men, and in men neither gassed nor wounded. This fact is useful in again drawing attention to the real significance of functional disorders in gassing. Gas was as potent as high explosive shell in the production of these disorders. Yet the pendulum may swing too far to the other side. The recognition of the frequency of functional manifestations following mustard gas led to a tendency to regard symptoms as functional until proved to be organic. However useful such an attitude proved in diminishing wastage, it must be received with caution. In most cases, for example, cough is clearly referable to the presence of organic lesions in the respiratory tract. In a small group, however, the cough is persistent and severe, although a careful examination fails to reveal any organic lesions whatever, which is not the same thing as excluding such as a possible cause. This cough is regarded by some of us as possibly functional. It had certain well-defined characteristics:

(1) It had a peculiar hard, ringing quality, easily recognized.

(2) It was of the unproductive type: repeated coughing brought no relief.

(3) It was troublesome chiefly at night, often causing serious loss of sleep, and was often paroxysmal.

(4) The sputum, if any, consisted of a thin, watery fluid of a very low albuminous content. This cough was very intractable, persisting long after all obvious signs of inflammatory trouble had cleared up.

Part II. Organic Effects.

Respiratory Tract.

Larynx.

All degrees of laryngitis were encountered from the slight case with hoarseness and painful cough to a grave condition associated with the formation of a false membrane.

Table III represents the relative frequency of the laryngeal complications.

Table III.

	1500	Percentage
Total number of cases		
Slight laryngitis	115	7·6
Severe laryngitis with complete or partial aphonia	81	5·4
Definite ulceration of vocal cords	22	1·4
Functional aphonia	108	7·2

No case was evacuated to England on account of laryngitis alone, unless ulceration of the cords was present.

False membrane formation. Capt. Shaw Dunn, referring to the graver type of case and basing his remarks on sections submitted to him by Capt. Ingram, wrote to us: 'The initial damage caused by this gas falls mainly on the trachea and bronchi, causing destruction of epithelium and copious exudation of a coagulable fluid which forms destructive casts.' Of 21 necropsies, in 8 a false membrane was found lining the whole length of the trachea, in 4 it was rather less extensive, and in 2 was confined to the neighbourhood of the cords; in 7 no membrane was found. It was, as might be expected, commoner in the group with an early fatal conclusion (it was present in all our cases dying on or before the fifth day), but a false membrane was found extending the whole length of the trachea in cases dying on the twelfth (two cases), fifteenth, and seventeenth days. The diagnosis was not difficult: moreover, it was of some importance, for in no other complication of mustard poisoning were appropriate measures of relief so well rewarded; these measures, though their immediate action was local, were taken with a view to avoiding the exhaustion, which is the sequel of the struggle to get air into the chest and has no small influence on the final issue.

All degrees of respiratory obstruction were noted; with the formation of an

extensive membrane the picture became unmistakable. The face was anxious and frequently cyanosed: the patient apathetic or very restless: his efforts were entirely concentrated on the business of getting air into his chest. The breathing was shallow and laboured, with sometimes a distinct stridor. Paroxysmal attacks of dyspnoea were not uncommon. The cough had a peculiar brassy quality, but might come on in spasms ending in a crow; in the worst cases it was gradually lost and there was little expectoration, but at first casts of the tubes and trachea were brought up in the sputum. On examination there were, perhaps, white patches on the uvula and tonsils; the movement of the chest was limited, there was inspiratory sucking-in of spaces, and very little air could be heard entering the bases. Gurgling râles were present at the base and in the axilla. In the final stages cough and expectoration were absent, a throat rattle was audible several beds away, the patient was delirious and attempted to get out of bed, and the accessory muscles were all brought into action in the vain effort to force air past the obstruction.

Bronchitis and Broncho-pneumonia.

Infection seems to follow very frequently on the destruction of epithelium in the trachea and bronchi: it spreads by the bronchi. With or without the signs of formation of false membranes, signs of bronchitis or broncho-pneumonia may then appear. In Table IV, of 692 cases admitted during four months 14 per cent. developed a severe bronchitis or broncho-pneumonia, causing prolonged retention in hospital with eventual evacuation to England, or, in a few cases, death.

TABLE IV.

This table shows the proportion of all Mustard Gas cases admitted during four months, in which were noted (i) *A definite pyrexia* (*apart from trifling initial reaction*), (ii) *Bronchitis and broncho-pneumonia, and* (iii) *Definite burns* (*apart from slight erythemas and scorching*).

			%	Total. %
	Total Number of Mustard Gas Cases	692		
Pyrexia	(*a*) Definite pyrexia, but mild in type, and not sufficient to cause long retention . . .	181	26	37·4
	(*b*) Severe, causing delay in hospital beyond a month, as from severe burns, broncho-pneumonia, &c.	78	11	
Bronchitis, &c.	(*a*) Milder types, not causing retention in hospital beyond a month	71	10	24·2
	(*b*) Severe bronchitis, broncho-pneumonia causing prolonged retention in hospital, evacuation to England, or death	97	14	
Burns	(*a*) Lesions not severe enough to cause retention in hospital beyond a month	116	17	31
	(*b*) Severe, causing prolonged retention in hospital, evacuation to England, or death . . .	98	14	

The distinction between bronchitis and broncho-pneumonia in gas poisoning is artificial. In 22 necropsies consolidation was absent in only 4. These were early fulminating cases that died on the second, third, and fourth days after

gassing; with the exception, therefore, of a small group of capillary bronchitis which includes those fulminating cases, we can safely affirm that in a severe case of mustard poisoning, where the main trouble is in the chest, consolidation is always present. Whether the signs of consolidation are detected depends on the focal distribution of the lesions. There are few features of interest in the signs and symptoms; cyanosis occurred in 42, haemoptysis in 20, well-marked toxaemia in 33.

We were familiar with an interesting small group with signs like those of a lobar pneumonia, attributable in two cases at least to the pneumococcus. The course was curiously benign, and it was not a little remarkable how little discomfort these patients experienced with extensive areas in both lungs over which loud bronchial breathing, free from adventitious sounds, was heard. The point arises, were these cases examples of lobar pneumonia? We can only answer that in the whole series, in all cases which came to a necropsy, the lesion was frankly broncho-pneumonia, and that, if lobar pneumonia does occur, it always ends in recovery.

These signs were usually found as early as the second, third, or fourth days, but in one case it represented a late secondary infection, so common in severe mustard casualties.

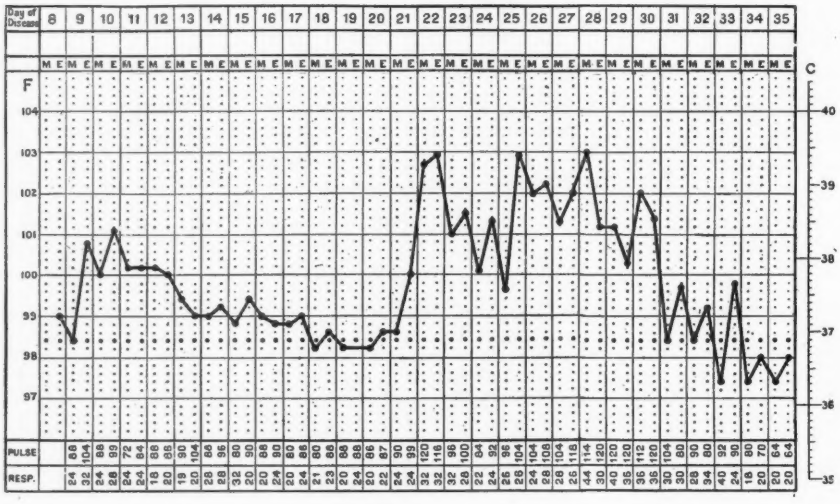


CHART I.

Case II. The initial lesion in this patient was broncho-pneumonia, mild in type, and the temperature from the fourteenth to the twentieth day was practically normal with little sputum. On the twenty-first day there was a sharp rise on the chart in pulse, temperature, and respirations. The patient looked ill, his breathing became distressed, and there was the typical grunt of lobar pneumonia. Bronchial breathing was heard over a wide area of the back and the fever fell abruptly by crisis, accompanied by profuse sweating. The signs cleared up rapidly, and in a few days the sputum amounted to only 1½ oz. in the twenty-

four hours. This man was boarded permanently unfit six and a half months after date of gassing.

Such a case suggests an analogy to MacCallum and Cole's (3) cases of pneumonia following measles. 'In measles,' they write, 'broncho-pneumonia may develop (with rise of temperature, &c.) three weeks after the fall of temperature, associated with the appearance of a rash, but in such cases there was not in the apyretic interval a complete disappearance of symptoms referable to the respiratory tract.' They concluded from this 'that the infection as well as lesion is probably a descending one, and that no sharp line can be drawn either in time or symptoms between the occurrence of the pharyngitis, laryngitis, bronchitis, and, finally, the bronchiolitis and broncho-pneumonia.

Pleurisy.

Pleurisy is a very common event in the group with severe pulmonary lesions. In those cases where the chart shows a relapse, the appearance of a new infection, or the extension of a descending infection, is usually marked by pleuritic pain, and a rub is often heard before other signs develop. Pleurisy was found in 14 out of 22 necropsies.

There was one case of empyema in this series (streptococcal): the man was eventually graded permanently unfit six months after his gassing. He now complains of dyspnoea on exertion, but is not otherwise much troubled, but there is a liability to bronchitis from which he had never suffered before gassing.

Abscess Formation and Necrosis.

'Infection', Capt. Shaw Dunn writes in his report on Capt. Ingram's sections, 'seems to follow very frequently on the destruction of epithelium in the trachea and bronchi, and it spreads by the bronchi, causing the suppurative changes which appear in most of your cases. In the worst type the infection acquires high local virulence, probably because the organisms obtain unimpeded growth inside the fibrin plugs, which protect them (as does a sequestrum of bone, for example) from the action of leucocytes. The result is focal necrosis of bronchiolar walls and of surrounding areas of pulmonary tissue: this may spread to form larger lesions.

'In your human material the primary effects of the gas on the bronchiolar walls appear to penetrate less deeply than I frequently see in animals: in experimental animals here (at Porton) there is often deep cauterization of the connective tissues of the bronchi as well as destruction of epithelium. Probably in the human cases the subsequent bacterial infection plays a greater part than in the lower animals.'

Frequency. In a consecutive series of 22 post-mortem examinations, necrotic changes were present in the broncho-pneumonic patches in 10, while actual abscess formation occurred in only 4.

Diagnosis of abscess formation in lungs in mustard poisoning. A diagnosis during life of abscess was made in one of the four cases.

Case III. This was in a man who was admitted to the hospital on the second day after gassing and who died on the eighteenth day. Broncho-pneumonia was diagnosed on admission; the signs were most marked in the right axilla and at the base; the only signs of bronchitis were heard over the left lung. The case belonged to the more serious type of casualty, but the course at first seemed to point to ultimate recovery. The first warning of coming trouble was a considerable diminution in the amount of daily sputum about the sixth day, always a grave sign in mustard cases when accompanied by no amelioration of the patient's condition. On the fourteenth day the sputum was noticed to be very offensive and 'wandering' began to be recorded in the night report.

The signs had not greatly altered since admission. A fan-shaped area of dullness extended from the spine across the middle of the right lung, the note in the right axilla was also impaired. In this axilla the bronchial breathing heard on the second day was no longer present, but there were some bubbling râles. From the analogy to other cases it was thought that some of the broncho-pneumonic areas had become necrotic. A skiagram taken on the seventeenth day by Major E. K. Martin showed a shadow running transversely across the middle of the right lung and closely corresponding with the fan-shaped area of dullness noted above. On examining the patient next morning, the right side of the chest presented the classical signs of pneumothorax. On aspiration extremely offensive gas escaped under pressure. An attempt was made without success by exploration with a needle under gas and oxygen to locate the abscess that had been diagnosed; the fourth rib was then resected by Major Martin. No abscess was found, but the diaphragm was covered with thick lymph. The right lung was adherent to the wall posteriorly and completely collapsed. A counter opening was made through the lower intercostal spaces and the chest drained. The patient died nine hours later.

Post mortem a small abscess cavity, the size of a two-shilling piece, was found under the right pleura; it had burst through it, giving rise to a pneumothorax. The shadow in the skiagram corresponded to a broncho-pneumonic area, small areas of which were necrotic. No part of the left lung sank in water. This was the only example of pneumothorax in the series.

In the three cases in which an abscess, unsuspected during life, was found at the necropsy, no typical signs of abscess were present during life. Tuffier, writing before the war, estimated that an abscess of the lung is situated in the lower lobe in 80 per cent. of the cases, but in this series the left upper lobe was in all three the seat of suppuration. There was little to help in diagnosis, no febrile recrudescence after a decline, for two of the patients died on the twelfth day and the third on the thirteenth, their charts in no way characteristic—no sweating, no signs of cavity. In one case a small quantity of foetid sputum, like anchovy sauce, was expectorated. In brief, in our experience, the only prospect of arriving at a diagnosis of abscess before death was provided by a routine examination of the sputa of all toxaemic cases for elastic tissue.

Gangrene.

In this series only one case of gangrene of the lung occurred. This man was admitted to the hospital on the second day after gassing, when he was already in an apathetic state. The signs of toxaemia increased and on the fifth day he lay in a torpid condition, bringing up sputum when raised to a sitting position; otherwise it was retained in the mouth. On the thirteenth day the

cough reflex was lost, but when the patient was turned on his side, he emitted rather than coughed considerable quantities of thin, intensely foul brownish-yellow sputum, which was found to contain elastic tissue. The foetor was so great that it was very unpleasant to approach the bed. The temperature oscillated between 101° and 103°, but the respirations were fairly constant between 28 and 32. The patient died on the fifteenth day.

The diagnosis was confirmed at the necropsy.

Bronchiectasis.

Frequency. We cannot say with any degree of accuracy in what proportion of cases bronchiectasis was present. On the one hand we have not yet the data that will enable us to determine in what number of late cases, seen in England, especially in connexion with the assessment of pensions, chronic bronchiectatic lesions are the basis of disability; on the other, acute bronchiectasis is readily overlooked in the febrile phase of mustard poisoning. In this phase it was associated with bronchitis and broncho-pneumonia, and the signs of bronchiectasis were commonly masked by those of these conditions. It is indeed rarely possible to diagnose bronchiectasis at this stage by examination of the chest; the type of pyrexia and the nature of the sputum were more likely to lead to the discovery of an unsuspected bronchiectasis. When we became aware later that this association of bronchiectasis with a particular variety of fever and sputum had been overlooked by medical officers, we could not but feel that the frequency of bronchiectasis in gassing is not fully reflected in our figures.

Of twenty-four post-mortems a very marked degree of bronchiectasis was noted in three. In one, where the necropsy was carried out on the thirteenth day after gassing, the lowest lobe of the right lung showed very beautifully an advanced bronchiectasic condition; in another, at the post-mortem on the fifteenth day, the bronchiectasis was found to be associated with gangrene of the lung; in the third, who died on the fifty-sixth day after gassing, a saccular bronchiectasis was confined to the left lower lobe.

In our experience bronchiectasis was a rare event in cases that recovered. But, for reasons given, it was in all probability commoner than our figures indicate, and, in particular, it will be interesting to follow the after-histories of those men in whom signs long persisted at one base, for they were not a few who lived, whose signs while with us were precisely the same as the case, recorded above, that came to the post-mortem table on the fifty-sixth day.

Bronchiectasis, as it was seen in hospitals in France, was an acute condition. In the patient Chart No. II, the diagnosis was made on the third day, and in another case, Chart III, on the sixteenth day. In the necropsies, carried out on the thirteenth and fifteenth days after gassing, the condition was fully developed.

Bronchiectasis was present to a marked degree in 1 per cent. of all cases admitted to No. 7 Stationary Hospital. This figure, we repeat, is an under-estimate.

(1) *Sputum.*

Diagnosis. This has a peculiar post-mortem room odour, quite unmistakable, and, in our experience of gassed patients, confined to those with bronchiectatic lesions. But if the sputum is collected in a cone-shaped glass, the distinctive odour may be masked by a top layer of tenacious, non-smelling bronchitic sputum; if this is decanted, the underlying, typically smelling, bronchiectatic element of the sputum pours like pus, in marked contrast with the viscous band, which at first flowed away in one broad continuous ribbon.

Characteristic as is the odour, it may well have been overlooked in wards containing at any one time 400 gassed men, by medical officers who omitted to bear in mind the possibility of bronchiectasis and to search for evidence of its presence. Microscopically this element of the sputum consisted of pus cells. In six consecutive cases diagnosed bronchiectasis the daily amount of the sputum varied between 230 and 720 c.c. It was tinged with blood in three out of six cases.

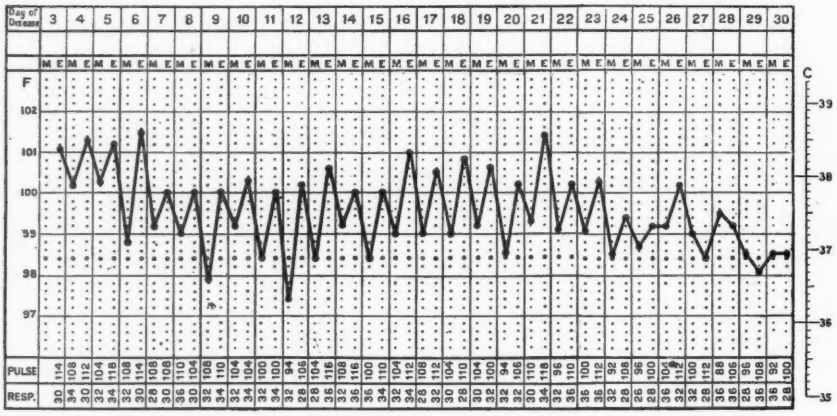


CHART II.

(2) *Temperature Chart.*

The chart is quite typical, though septic burns will give a very similar picture. It is a swinging pyrexia with often a difference of two degrees between the morning and evening readings. In Chart II the morning temperature was 98·4° F. to 99° F. and the evening 100° to 101°. In Chart III (a severer type) there is a similar oscillation, but the morning base line is now in the neighbourhood of 100°. The duration of the fever is seen in the charts.

(3) *Signs.*

In all the examples of bronchiectasis in our series, both in those where a necropsy was performed and in those which ultimately recovered, the condition was accompanied by broncho-pneumonic consolidation and bronchitis; pleurisy

was also present in the majority of cases. Accordingly it was not often possible to diagnose the bronchiectasis on the physical signs alone. For example in a patient admitted moribund on the twelfth day, the physical signs, exactly alike at both bases, consisted of an area of dullness and bronchial breathing without adventitious sounds. Yet post mortem the condition found at the two bases was very different. The left lower lobe presented on section numerous solid areas arranged like fruit on a tree, and in the centre of many of these areas there were necrotic patches. In the right lowest lobe the bronchi and bronchioles were markedly dilated and the lining membrane was ulcerated. The bronchiectasis existed to such an extent that the bronchi appeared to fill the greater part of the lobe. The lung substance showed numerous necrotic areas and the whole lobe presented a degenerate mass of breaking-down substance, which sank in water. It was not possible in this case to diagnose the addition of an advanced condition of bronchiectasis to necrotic broncho-pneumonic areas.

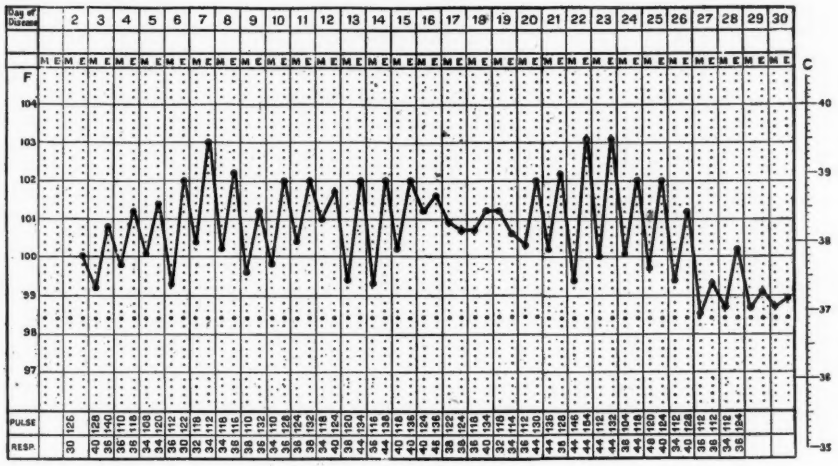


CHART III.

Pulmonary Apoplexy.

Case IV. Admitted on the third day with severe septic burns. For the next four days the patient lay in a somnolent toxic state and, on examination of the chest, few abnormal signs were found. On the ninth day the pulse became weak and irregular; the patient had been delirious for twenty-four hours, and this continued till death. On the tenth day the breathing was very hurried and the sputum was tinged with blood; there was extreme thirst and the pulse was 150. Death occurred during the afternoon.

At the post-mortem examination a fresh and extensive haemorrhage, the size of an apple, was discovered at the base of the left lung; in this red clot there were no signs of organization. Capt. Sarmento, of the Portuguese Medical Service, has shown us a lung, taken from a man gassed with mustard, with a very similar haemorrhage.

A Note on the Bacteriology.

MacCallum and Cole, working on pneumonia associated with measles, found that the high incidence of pneumonia in their hospital was due, to some extent at least, to infection occurring within the hospital itself. 'The number of carriers of a haemolytic streptococcus', they write, 'increased with the time in hospital, a large percentage acquiring the streptococcus in their throats for the first time during their stay in the wards.' They concluded that the high incidence of broncho-pneumonia during convalescence from measles is directly related to the transfer of the infectious agent from one patient to another in the wards of the hospital. Infection started in a ward, the streptococci became widely distributed, gaining in virulence with repeated transfer through the human subject, and serious and widespread infection resulted.

In gassed patients raw surfaces existed, facilitating the invasion of the respiratory mucous membrane by micro-organisms, and with this idea in our minds we had resorted to the periodical disinfection of the acute ward, with apparently happy results. The publication of MacCallum and Cole's work lent support to this theory, and we believe that a similar practice has been followed by some French workers. The subject of ward infection is of some importance and requires further investigation.

The routine of a large hospital with only one bacteriologist laid down the limits within which investigation into the secondary infections in gassing was necessarily confined. Blood-cultures were taken by Capt. Ingram during life and also after death from the organs and tissues, and the sputum coughed directly from the lung was examined in a certain number of cases; but this number was not large, and many interesting questions remained unanswered.

The respiratory rate varied apparently with the infection and seemed strangely independent of the extent of lung substance involved; but we were not able, as we had hoped, to throw any light on this, nor are we in a position to classify the different groups of the respiratory type according to the causal organism. Our knowledge of the bacteriology of mustard poisoning is left in a provokingly incomplete state.

Charts to show Relation of Temperature to Quantity of Daily Sputum.
Continuous black line—sputum curve. Dotted line—temperature curve.

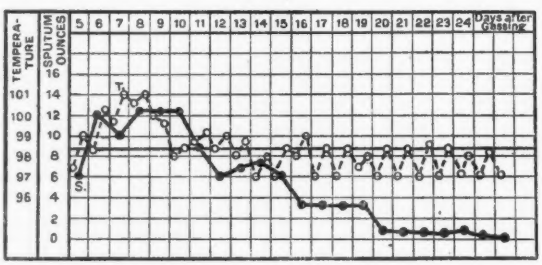


CHART A. *Typical sputum curve of mild case of Broncho-pneumonia after Mustard Gas poisoning.*

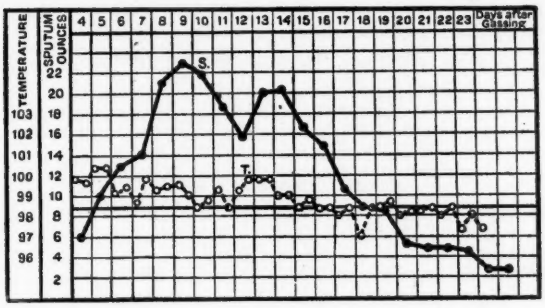


CHART B. *Typical sputum curve from a mild case of Broncho-pneumonia.*

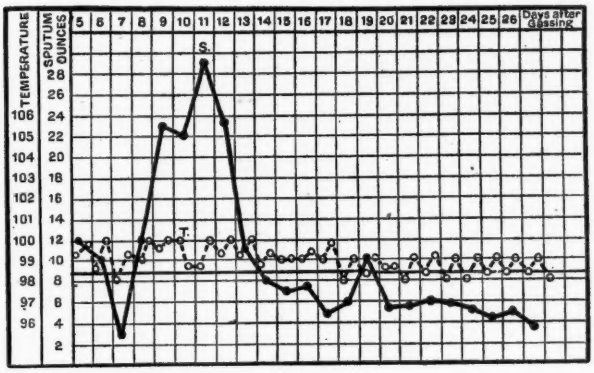


CHART C. *Case of Broncho-pneumonia.*

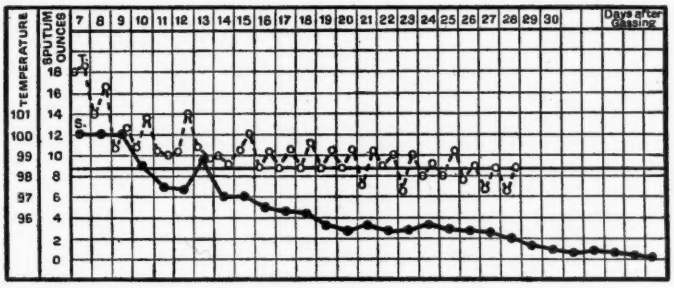


CHART D. *Case of Broncho-pneumonia.* This chart could be completed to show rise in temperature without corresponding rise in sputum cases which followed femoral thrombosis.

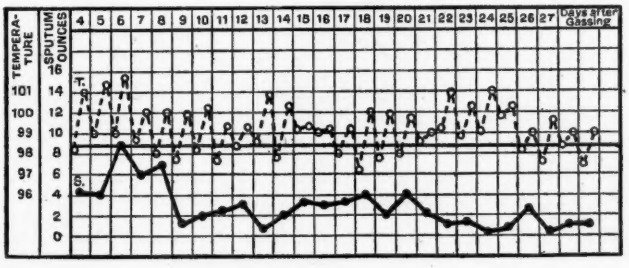


CHART E. Case where temperature was sustained by septic burns. Chest condition not severe.

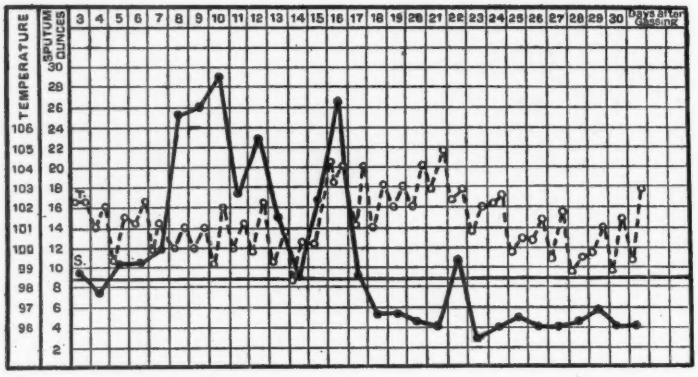


CHART E 1. *Case of Empyema after Mustard Gas poisoning.* Fall of sputum not accompanied by fall of temperature, which was kept up by empyema.

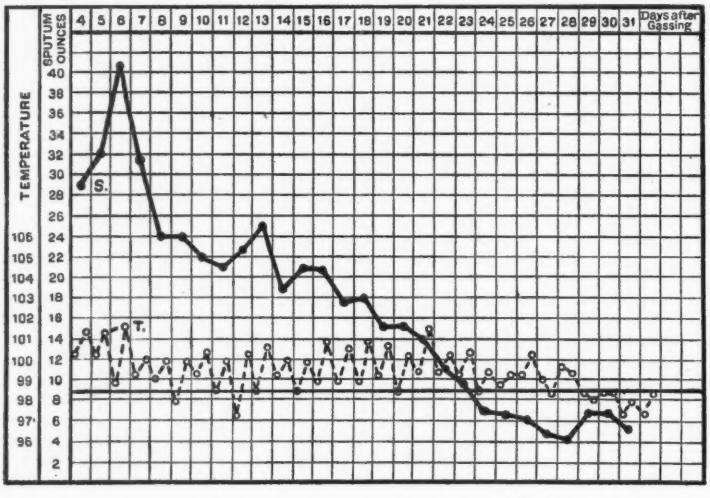


CHART F. (Same case as Chart II in text, p. 214.) *Case of Bronchiectasis after Mustard Gas poisoning.*

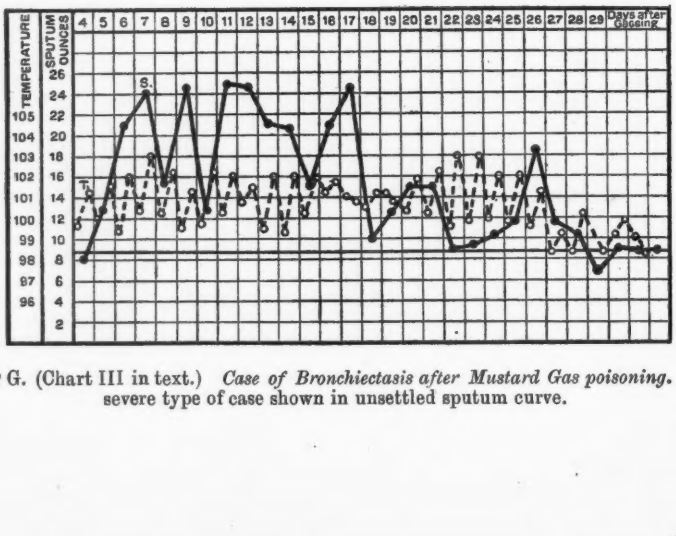


CHART G. (Chart III in text.) *Case of Bronchiectasis after Mustard Gas poisoning.* A very severe type of case shown in unsettled sputum curve.

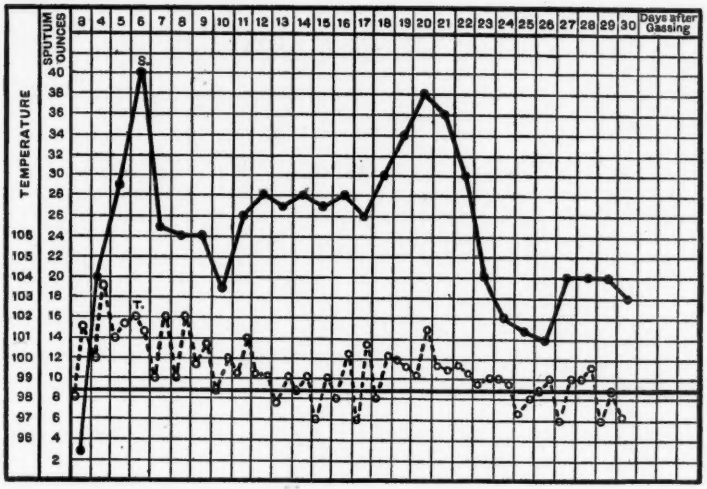


CHART H. *Showing very severe case of Bronchitis and Broncho-pneumonia.* Note sputum remains high when temperature falls. In these cases this was a reliable warning of future trouble. After 14 days of apyrexia temperature again rose and death occurred on 59th day.

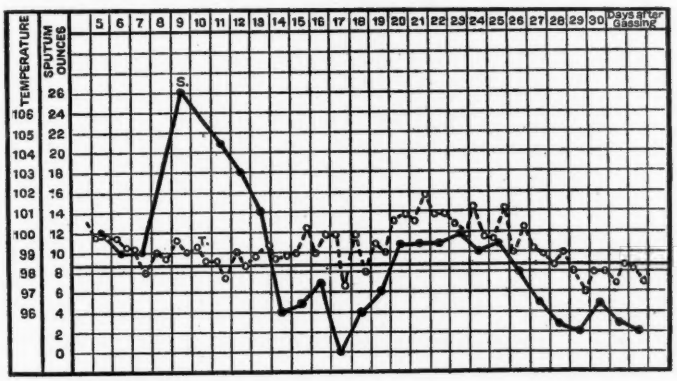
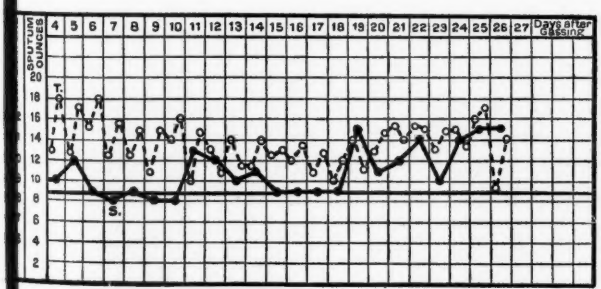


CHART I. *Showing secondary rise in sputum curve accompanying secondary rise in Fever.*



HART J. *Shows relation between temperature and amount of sputum.* Case recorded in text with death on 50th day. Post mortem acute and chronic pneumonia present.

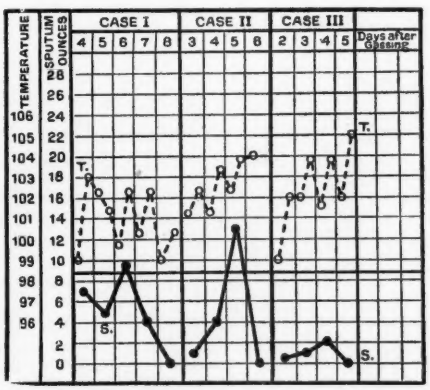


CHART K. Three charts of cases dying on 8th, 6th, and 5th days, showing (*a*) small quantity of sputum in such cases, (*b*) fall in quantity as cases went to the bad.

Effects on the Eyes.

The eye lesions are of interest from three points of view—

(1) Effect on period of invalidism.
(2) Effect on morale of patients.
(3) Permanent effects.

There were two groups—

(1) Slight conjunctivitis requiring only about fourteen days' treatment in hospital	767	cases.
(2) Severe lesions	352	„
Total number of mustard casualties in which eyes was affected or 74·6 of all cases.	1,119	„

The lesions in the second group were of three degrees of severity—

(1) Severe conjunctivitis with photophobia and lachrymation in	253	cases
(2) Acute purulent conjunctivitis without corneal injury . .	69	„
(3) Acute purulent conjunctivitis with corneal injury . . .	30	„

Permanent effects were seen only after injury of the cornea. When the cornea escaped, functional photophobia was the main cause of detention in hospital. The effect of these eye lesions on the morale of the men is described under Functional Nervous Disease. It is, indeed, very remarkable how constantly men complain of their eyes in England months after gassing, and when no signs can be found either in the eye or elsewhere.

Gastro-intestinal Tract.

The Comparative Immunity of the Gastric Mucosa.

Vomiting. While a history of retching and vomiting can be obtained from the great majority of gassed patients as one of the earliest manifestations, persistence or recurrence of vomiting after the first day is unusual. In this series of 1,500 cases, excluding 16 instances of hysterical vomiting, only 13 examples were collected. Of these in 8 the vomiting occurred within the first 48 hours in patients who had been severely gassed, and in whom, probably, the initial gastritis was responsible for the vomiting; the remaining 5 gave a history of having drunk contaminated shell-hole water: they were mild casualties, and within a week were convalescent. In the absence of a post-mortem examination, it is not always possible to determine the precise significance of this symptom in mustard gas poisoning. In some the vomiting is the expression of the initial acute gastritis, resulting from the swallowing of saliva containing mustard gas in solution; in others it may be due to coughing and to the tickling caused by an oedematous uvula; when the vomiting persists or recurs after the first few days it has rarely an organic basis, and is frankly hysterical in origin.

Passing over the initial vomiting which occurs before a patient's admission

to a Casualty Clearing Station or within a few hours after his admission, the symptom is, in our experience, rare indeed. Including examples of hysterical vomiting it was present in less than 2 per cent. of the cases in this series. But, since some importance has been attached to this symptom by workers in English hospitals, and since the French authorities take up a different attitude as to its significance, it may be well to review the evidence that exists of a definite lesion of the stomach wall.

French views (4). The digestive system, in their experience, 'frequently participates in the syndrome; gastric pain and discomfort and diarrhoea, often bloody, help to weaken the patient, and when there is a general affection of the skin produced by mustard gas and not a purely local one, the digestive apparatus is always involved'. Post-mortem examination, they contend, shows that, at least when there is absorption of the vapour, the lesions of the digestive tube are sufficiently marked to account for these symptoms. The gastric mucosa has lost its sheen and is of a darkish red colour; ecchymotic areas, sometimes true ulcers, are found, especially on the greater curvature and in the neighbourhood of the pylorous. In this case the contents of the stomach are blood-stained.

German views (5) are mainly based on casualties occurring in the production and use of mustard gas on an extensive scale, and naturally lay stress on *burns*. Indeed, their clinical description of these burns is the most complete and accurate that we possess. If then there is anything in the French contention that the digestive apparatus is always implicated when there is a general affection of the skin, we might reasonably anticipate that, in the enemy literature, wherein the results of the burns incurred in the manufacture and handling of shells overshadow the effects of inhalation, gastro-intestinal symptoms would play no small part. But it is quite otherwise.

They were aware from experiments on animals that the vapour of mustard gas may penetrate the lungs when inhaled and, in addition to its local effects, cause certain general effects on the body after absorption, and that these may unite into a symptom complex characterized by reflex functional disturbances of the circulation, the nervous system, and the alimentary canal; but when it came to translating such a possibility into terms of actual clinical experience, they were content to dismiss the subject with the observation that 'the illness is occasionally accompanied by digestive troubles, such as pain in the stomach, diarrhoea, and vomiting, or obstinate constipation'. 'It is not certain', they add, 'whether a sufficient quantity of the poison can be absorbed from the human skin into the interior of the body to give rise to the disturbance of general metabolism that we have noted in animal experiments, but one must bear this possibility in mind.' Surely a significant admission when we reflect on the exposure of their workmen in the factory and of their gunners in the field.

It remains to set forth our own experience based on clinical observations on 1,500 consecutive cases of mustard gas poisoning and on 24 post-mortem examinations. Three of the patients died before the initial vomiting had ceased. Capt. Shaw Dunn wrote to us that there was certainly no gross lesion in the sections

examined. He adds that he has once or twice seen miliary ulcers in the stomach in monkeys after mustard gas, but that they are not frequent.

The clinical evidence has already been recorded. It is interesting to note that of the eight cases in which the initial vomiting was prolonged, six were extensively burnt and presented other signs confined to the more serious type of casualty. In one of our early cases with this initial severe and prolonged vomiting the patient continued to vomit bile-stained fluid at intervals of about three hours till his death on the third day. The day before death this fluid was mixed with dark coffee-ground material. Unfortunately, no sections were taken.

Intestine.

French views. There is, they write, often pain in the epigastrium. The pains do not remain localized to the epigastrium, they extend all over the abdomen, they are often very sharp and are followed by diarrhoea, with foetid and blood-stained stools. In the following days the pains may cease, diminish, or persist: in the last event the diarrhoea persists and melaena may appear. This is always a grave sign: usually constipation is noted and the intestinal manifestations are slight. Post mortem the intestine is often affected. Towards the end of the jejunum and in the ilium oedematous segments of bowel, infiltrated and congested throughout their whole thickness, may be found. On opening, the mucosa is ecchymotic, sometimes blood-stained. The large intestine is more rarely affected: the lesions are usually situated in the rectum, and ulcerations and false membranes of dysenteriform aspect are described. Such marked lesions are only found in grave cases, tending to a fatal result. Most frequently, there are only congestive and oedematous lesions which steadily disappear.

German views. Among the rarer symptoms the Germans mention diarrhoea or constipation. 'Haemorrhage into the intestinal mucous membrane, as well as inflammatory exudation in the lumen of the intestine, have been found at autopsy.'

Clinical evidence. There was little evidence of any serious intestinal derangement in our series. Diarrhoea was present in 48 cases during their stay in hospital. An initial diarrhoea was not uncommon, but this passed off in a few days. In later cases it was sometimes present, but not more frequently among gassed casualties than in the ordinary medical cases of the other wards. Even in the gravest cases of gas poisoning diarrhoea or any sign of gastro-intestinal disturbance was uncommon after the first few days. The only patients in whom it formed a definite feature of complaint were those in whom the poisoning was due to drinking of contaminated shell-hole water. All these cases were mild, and showed no conjunctivitis nor other evidence of exposure to the gas.

Two patients were admitted in the autumn of 1919 complaining of diarrhoea, which commenced with mustard gas poisoning and continued at intervals for many weeks. Both patients were negative to the dysentery and enteric groups,

and neither of them had served in the East. In another man with irregular fever blood was noted in the stool a week after gassing. There was no mucus, but defaecation was painful. The pain gradually disappeared, but blood was still present in the stools when he was evacuated to England a week after the blood was first noticed. At this time nothing could be made out by rectal examination, but on abdominal palpation there was tenderness over the descending colon which was palpable. Abdominal pain was a much more frequent symptom. It was present in most of the severer cases, and was presumably due to coughing. Of the milder cases it was noted in 75. It was usually situated in the epigastrium, or just above and to the left of the umbilicus. It was never associated with any sequelae, and seldom persisted beyond the first week. In thirty cases (2 per cent.) it was the burden of the patients' story. Abdominal tenderness after the first day or two was exceptional.

Nervous System.

A state of mental excitement, accompanied by a noisy delirium, was noted in one case recorded elsewhere. In another, with very extensive septic burns, there appeared to be a profound disturbance of the nervous system, with tremor of the hands, exaggeration of the superficial and deep reflexes, and hyperaesthesia of the skin. These cases stood apart in our series, though every variety of functional nervous disorder was seen.

The Blood.

The leucocyte count rose sharply with the advent of broncho-pneumonia, and in such cases a fall without any improvement in the patient's condition was an unfavourable omen. Matthew Stewart (6) has published similar results, which are, of course, in no way peculiar to the broncho-pneumonia following gas poisoning.

Femoral thrombosis occurred in two patients; in one, where the initial fever was due to broncho-pneumonia and to severe burns, cardiac dilatation was noted on the eleventh day, and the patient was in a state of toxic somnolence. The temperature had begun to fall on the seventh day, but did so with reluctance, and a long smoulder ended on the thirty-first day in a sharp rise, accompanied by the signs of femoral thrombosis. The left calf measured one inch more than the right. Citric acid in 30 gr. doses was given four-hourly: the fever rose gradually and declined in the same manner over a period of ten days, but the chart continued to show a pronounced smoulder, and this was still present on the sixty-seventh day. The patient was sent to England, and was graded as permanently unfit. He went to Australia, where we were unable to keep in touch with him.

Blood Pressure.

Capt. S. Fraser has recorded the systolic and diastolic pressures in a considerable number of our cases; his results have been largely negative. In

the cases that were rapidly fatal the systolic readings rose steadily from about 130 to 160 or 170.

The Kidneys.

Frequency. In the French literature stress is laid on the urinary changes. These they regard as the most conclusive evidence of their contention that in all mustard casualties of any degree of severity there is a 'general poisoning of the system'. Their views are summarized in the *Notice clinique et thérapeutique de l'intoxication par les gaz*, May, 1918, as follows:

'In the serious cases albuminuria is almost constantly present. The albuminuria, if it reaches a marked degree and persists, is a grave sign. It has a true prognostic value. Whilst the initial albuminuria of intoxication by suffocating gases is ephemeral, and is only the expression of a passing congestion of the kidneys, albuminuria in those poisoned by mustard is an indication of an affection of the renal epithelium: it is frequently accompanied by the presence of casts in the urine and may last a long time. Autopsy, in cases of general intoxication, shows congestion, desquamation, and in places necroses of the uriniferous tubules.'

Our experience supplies no confirmation of these views. On the contrary, it provides evidence, clinical and pathological, which is in strange conflict with their data. The presence of albuminuria is very rare in mustard gas; in some cases a trace is found on boiling the urine, but the number of such cases is no greater than in a series of controls taken from non-gas cases. A degree of albuminuria beyond a mere trace on boiling was certainly confined to the most severe type of gassed casualty, but in 1,500 consecutive cases only 30 examples were collected. Of these 16 were associated with severe mustard burns; in 3 the onset of albuminuria was related to the development of a complication such as empyema, or abscess of the lung; in 5 it was a terminal event; in 2 it was associated with cystitis; while in 4 it appeared to a moderate degree in patients with severe pulmonary lesions. In our series it was always associated with profound bacterial infection.

The French claims with regard to the value of albuminuria in prognosis were equally at variance with our results. In the majority of the fatal cases the urine is free from albumin up to the time of death, while in a few cases where it has been a marked feature recovery has followed.

Post-mortem evidence. Post-mortem examinations by Capt. Ingram confirm the conclusions based on clinical grounds. In the absence of extensive burns that have become sceptic, there was no evidence of an affection of the renal epithelium, nothing beyond congestion. Capt. Shaw Dunn has kindly examined sections of the kidneys taken from eighteen necropsies and submitted to him by Capt. Ingram for his opinion.

'In nearly all the cases, fifteen out of eighteen,' he writes, 'there is marked acute congestion, especially of the glomeruli. This has no specific significance, as it is almost always present with other gases.'

In three he found a condition of acute haemorrhagic nephritis with tubular haemorrhages. In one, who died on the fifth day, albuminuria was noted on the third day and till death. In all three the renal condition was associated with extensive and septic burns. The third case shows so clearly that a condition of haemorrhagic nephritis may arise in the complete absence of pulmonary involvement, the sequel only to septic burns, that the notes are here set forth at some length.

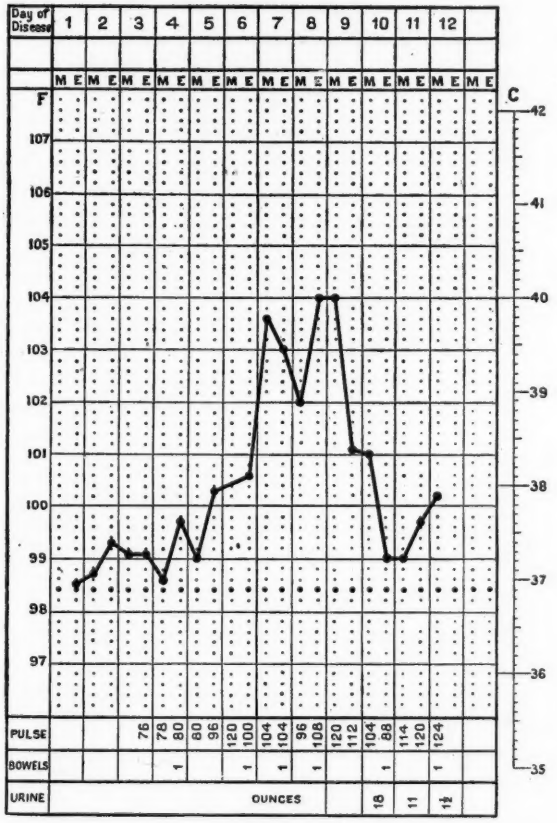


CHART IV.

Case V (Chart 4). Pte. N. H., aged 19, admitted to No. 7 Stationary Hospital on the second day after gassing. His card was marked by the Field Ambulance 'Lachrymatory', and, apparently consequent on this diagnosis, he was not washed nor were his clothes changed.

There was an extensive burn involving the whole back from the occiput to the buttocks, and extending laterally as far forward as the anterior axillary line. The flexor aspects of the arms and the extensor aspects of the knee were also burnt. It was estimated that from a quarter to one-third of the total skin surface was involved.

There was no cough, no conjunctivitis, no evidence then or subsequently, before or after death, that the gas had been inhaled. The temperature and pulse

were normal, and, in spite of the extent of the burns, experience of similar cases led to a cheerful prognosis; indeed, the patient was admitted by the receiving officer to a marquee reserved for the lighter gassed casualties.

On the seventh day the blisters changed into sloughs, there was a sharp rise on the chart to 103° F., and the gravity of the condition could no longer be overlooked.

The onset of the nephritis was insidious; it would have passed unnoticed had the smoky urine been overlooked. Throughout the illness there was no headache, no oedema, no uraemic symptoms except vomiting, which occurred about twice a day for the last three days before death, no difficulty of breathing till twenty minutes before death. This was due to heart failure; for the last forty-eight hours the pulse was uncountable and almost imperceptible. The patient was never unconscious, nor in any way mentally obscured till a quarter of an hour before the end.

Physical examination of the lungs forty-eight hours before death revealed no abnormal signs. The urinary secretion for the three days before death is shown on Chart IV, from which it will also be noted that the pronounced pyrexia began on the fifth day, and that the patient died on the twelfth day.

At the post-mortem examination made two hours after death the lungs were apparently normal; sections confirmed the absence of any pulmonary lesion. Capt. Dunn could find no change in the sections submitted to him, but in the renal sections he found an acute haemorrhagic nephritis with abundant tubular haemorrhages.

The insidiousness of the nephritis and the absence of uraemic manifestations were interesting clinical features, but the real significance of such a case is the conclusive evidence it supplies that a condition of acute haemorrhagic nephritis may be solely due to septic burns. In the three examples of this condition our post-mortem records provide, septic burns overshadowed the other results of gassing; our clinical material, too, strengthened the conviction that, with the exception of a slight albuminuria seen in a few cases, the expression of a passing congestion, the renal changes, when there are any, are due to burns which have not been treated as wounds, or unsuccessfully so treated. The unfortunate errors of judgment in this case, firstly, in diagnosis at the Field Ambulance, with the consequent omission of the usual precautions in washing and changing of clothes, and, secondly, in our early failure to recognize the gravity of the condition, probably precluded a happier issue.

Burns.

Burns, beyond a mere erythema, were present in 31 per cent. of all cases (see Table IV). Although the total number of cases is thus greater than that of chest conditions, a relatively smaller number of these were sufficiently severe to cause prolonged retention in hospital (14 per cent.). Of the 98 cases with severe burns, 34 (5 per cent. of all admissions) were sent to England; 7 died with or without

complications; and the remaining 57 were transferred to convalescent camps after a prolonged stay in hospital. In general, it was our experience that where burns were so extensive or severe as to give rise to fever of more than ten days' duration, and where there were obvious signs of septic absorption, evacuation to England was advisable. Milder cases were sometimes very slow in healing, but where there was no evidence of constitutional disturbance it was thought profitable to retain such cases.

Burns of the scalp and the genitals were the most troublesome, mainly because of the difficulty in cleansing them efficiently. The most intractable cases may remain in hospital for eight or even ten weeks. Boils on the site of burns, abscess in groin or axilla, with the mechanical results of burns when they involved the genitals, demanding circumcision, delayed some cases. An attempt was made to check the results of the various alternative methods of treatment by daily smears taken from the burns (Martin and Ingram), but little came of this practically, since the cases that caused delay were mainly burns of the genitals (318 of 543 in the whole series of 1,500), which were difficult to investigate bacteriologically.

We shall not describe the different stages in these burns (erythema, vesicle, slough), but wish to call attention to the association of burns with:

(1) Cardiac dilatation.

(2) Haemorrhagic nephritis (three cases).

(3) The very rare nervous manifestations: tremor, excitement, &c.

Enlargement of the Heart.

In a small number of the graver cases the well-defined maximum impulse of the heart was situated from 4½ to 5½ inches to the left of the mid-sternal line, in some in the sixth space. In one case the patient had several fainting attacks, and eventually died of syncope. The condition is uncommon after mustard gassing. In ten cases it was present to a very considerable degree, all but one were severely burnt, and four suffered from burns only, without any chest trouble. No case with involvement of the lungs but without burns has shown any appreciable degree of dilatation.

The interpretation of these observations is not easy; in one case only was venous engorgement noted, and none of the usual signs of cardiac failure were present. We can find no reference to the point in the scanty literature of the subject.

The 'Effort Syndrome' and Mustard Gas Poisoning.

Frequency. During convalescence it was noticed that a number of patients who had been gassed by mustard began to complain of fatigue, breathlessness on slight exertion, palpitation, and other symptoms, amounting, in some cases, to a definite 'effort syndrome'. Even in the mildest examples of gassing it was

not uncommon to find these symptoms. On this account a series of 100 consecutive mustard convalescents was observed with a view to determining to what extent the 'effort syndrome' was a cause of delay in hospital: to these a simple exercise test was applied and the response to effort noted. In the first week of convalescence (after the men left their beds during the day) as many as 30 per cent. gave an exaggerated response, but this number was rapidly reduced to 10 per cent. as the patients became accustomed to exercise. In a few symptoms persisted.

In the whole series of 1,500, 125 men failed at first to respond normally; they were retained for further observation and treatment, and later examined by the same test. Under this régime the great majority of the 125 cases gave a normal response at the end of a short course of treatment. In 19 men the symptoms of the 'effort syndrome' persisted in spite of graduated exercises. Of these in 9 the symptoms dated from a previous infection (trench fever in 7, rheumatic fever in 1); in 1 the symptoms had been noticed before the war; to 4 the unsatisfactory label of neurasthenia had been attached; in 5 the symptoms were apparently directly due to gas. We found then, that when care had been taken to fix the date of onset of symptoms with the object of eliminating such as were present before gassing, in only 5 patients in the whole series could the 'effort syndrome' be attributed directly to gas.

We concluded that the symptom complex known as the 'effort syndrome'—so common after phosgene poisoning and in other war diseases—is very rare after mustard gas poisoning, that when it does occur a previous infection is much more likely to be the causal factor than any effect due to mustard gas. This view as to the infrequency of gas as a provoking cause of the 'effort syndrome' is in accord with Dr. Lewis's experience at Colchester (7), but he qualifies his verdict in the light of recent reports by the admission that it may be more than an aggravating cause.

So much has been written around this vexed question of the frequency of the 'effort syndrome' after mustard gas poisoning, so conflicting has been the statement of facts, that it may be worth while here to consider the evidence.

In the reports to which reference has been made we read that symptoms of the 'effort syndrome' appeared in 30 per cent. of gassed men. This figure in our series represents the percentage of mustard casualties who give an abnormal response to effort in very early convalescence after a period in bed—the exaggerated reaction of the body to exercise in those who are in process of returning to complete health. The reaction, as we have seen, rapidly became normal with treatment in all but a few cases. But in these reports the figure is used in a very different sense. We have to reconcile two conflicting conceptions: we have to review the facts on which each is based, and the methods employed in eliciting those facts, to search for fallacies that we may determine which of two theories holds the truth, whether gas is extremely common as a provoking cause of the 'effort syndrome' or relatively unimportant. It is well first to look for the mote in our own eye.

During the war symptoms of the 'effort syndrome' in gassed men were noted:

(1) In patients who were kept in bed in France on account of the severity of the respiratory lesions, and who were evacuated to England as stretcher cases, the symptoms of the 'effort syndrome' appearing only after their arrival in England when they were got out of bed.

(2) In patients at Base hospitals in France who had been got out of bed and were detained with a view to transfer to a convalescent camp.

The figures in our series were at first drawn from the second group. This fact may at first sight go some way to explain the discrepancy between the two sets of figures. But during the last six months of the period reviewed in this paper cases of all degrees of severity were detained in No. 7 Stationary Hospital till they were fit for a convalescent camp, and it was not found that our early conclusions required revision to any appreciable extent. Incidentally, the interesting conclusion was established that the symptoms of the 'effort syndrome' are far commoner in the milder than in the more severe type of mustard casualty.

Of all mustard casualties arriving at the Boulogne Base only 14 per cent. were evacuated to England. It was found feasible to maintain that figure for many months. To all the rest a true crucial test was applied: they were after a brief period transferred through convalescent camps to duty. Since less than 1 per cent. was readmitted to hospital, if we do not include the exaggerated response to effort in the first few days of convalescence, the incidence of D. A. H. in all gas cases must be less than 14 per cent.

Therefore the 30 per cent. quoted of these English workers is not to be taken as the percentage of all gassed men in whom the 'effort syndrome' is present, but if accepted at all, as the percentage of a certain severe type of casualty that had succeeded in passing through the filter, which from the moment a man leaves his unit attempts to separate off those who will soon be available for duty. At the best the figure represents a percentage of a certain number of cases that had succeeded in reaching England, a number infinitely small in proportion to the total number gassed.

These considerations may be reinforced by criticism of the methods employed. One of us working in England since the armistice has had an opportunity of examining a number of men who had been gassed and were under treatment for D. A. H. on the lines responsible for these reports. They belong to two classes:

(1) A group in which the symptoms and signs of gassing were apparently so slight that the men never left their duty, only developing the 'effort syndrome' subsequently.

(2) A group in which the symptoms and signs were directly attributable to some previous infection, the gassing having acted as an aggravating cause, or had arisen in men who were confined to their beds for a considerable period with grave pulmonary trouble, the direct result of the gas.

In France we were familiar with these two classes. The second was a small group with a relatively unfavourable prognosis; the first was by far the larger group, and few of them were allowed by the authorities at the Boulogne Base to

leave France. To them, as we have said, the crucial test of return to duty was soon applied, and the results confirmed the favourable prognosis pertaining to this group.

The efficiency of No. 1 Convalescent Camp as a heart centre and the influence of Colonel Elliott in reducing the number of gassed men evacuated to England apparently gave to workers at Boulogne a somewhat one-sided view of what was happening. It was obvious from what we saw in England that these methods were far from universal, either at other Bases in France or in England.

Large numbers of the first group had, it seemed, passed through the filter and reached England; they had escaped the crucial test which the rest of their group had successfully passed, and were now under a very different *régime* in an advanced process of hospitalization. The 30 per cent., to which reference has been made, were apparently mainly composed of these men. We think it unnecessary to look farther afield for an explanation of the alleged frequency of the 'effort syndrome'.

This danger of hospitalization was a very real one. We are dealing in the 'effort syndrome', as Dr. Lewis has pointed out, with a very mixed group. He recognizes two large sub-groups, one marked by constitutional weakness, nervous or physical or both with imperfect development, the other comprising those who may be regarded as 'played out' by exposure and strain; for example, in the men labelled neurasthenia in this series the stigmata of the one sub-group was accompanied by the history of the other. In all there is a tendency to exaggerate symptoms, it is for ever necessary to check the subjective by the objective. Yet so potent is the fascination of this diagnosis of D. A. H. over some minds that the discovery of a soldier with a normal response to exercise became ever more rare. When the sane teaching of Colchester is generally heeded, these discrepancies in results will cease to exist.

Fever.

Table V.

Showing the Proportion of all Mustard Gas admissions for four months in which there was a Definite Pyrexia (apart from trifling initial reaction) during the period in hospital.

	Total Number of Mustard Gas Cases	692		
With pyrexia	(*a*) Definite pyrexia, but mild in type, and not sufficient to cause retention in hospital beyond one month	181	26 %	37 %
	(*b*) Severe, causing delay beyond a month, as from severe burns, bronchitis, and broncho-pneumonia, &c.	78	11 %	

Types of Fever.

Of mustard casualties with a febrile reaction there are two groups with two distinct types of fever.

(1) A broncho-pneumonic chart with a fairly constant temperature commonly lasting from the second, third, or fourth days to the tenth, eleventh, or even the fourteenth day. It may fall by lysis or by crisis. In some cases there is

subsequently an evening smoulder of about 1° F. for many days or even weeks; in others the fever, once it reaches normal, remains there.

(2) A swinging chart where the morning temperature is 99° or under and the evening figure above 100° for 2–4 weeks.

This is associated with a severe type of mustard casualty. It rarely ends fatally, but convalescence is prolonged; for example, in the records of a group of such cases before us the evening reading was consistently above 100° till the thirty-fifth, fifteenth, twenty-sixth, fourteenth, twenty-second, ninth, twenty-first, twenty-fourth, thirteenth, twenty-ninth, thirty-third, twenty-fourth, twenty-fourth, twenty-seventh day after gassing. It is associated with extensive septic burns or bronchiectasis, or possibly with necrosis following broncho-pneumonia, if such cases ever recover. This group is a relatively small one compared with the first, but it will probably bear a very different proportion to the total number of applicants for pensions, in whom there is reason to believe that there is a definite organic relic of gassing. As far as we are able to judge from following the subsequent course of these cases in England, this group has a relatively unfavourable after-history. They are, too, peculiarly liable to intercurrent disease.

With a little experience it was possible to read a mustard chart and to foretell with a fair degree of accuracy what would happen, or in a chart of a case not actually seen, what had happened.

In a certain proportion of the cases in group 1, after the initial fever had practically settled, the chart of convalescence was broken, perhaps weeks after the gassing, by a second bout of fever, representing either a ward infection or the extension of a descending infection. In either event, if the case came to necropsy, a broncho-pneumonia of two different dates was found, as in Case VI, where an acute and chronic broncho-pneumonia were both present. In such a case there was a corresponding rise in the pulse and respiration rate, associated with sharp pleuritic pain in one side, and later a rub with the signs of broncho-pneumonia. Chart I is an example of a case where the secondary infection ended in recovery; Chart V, where it resulted in the death of the patient.

In another case a new infection began on the twenty-seventh day with acute pain in the left side. This lasted for a week, and there was no return of the fever till the eighty-second day, when there was again sharp pain in the same side with high fever and signs of consolidation.

Broncho-pneumonia was diagnosed in one patient at the right base on the fourth day, and on the ninth day the breathing at this base was bronchial. The fever settled on the eleventh day, but there was a sharp return of pyrexia between the sixteenth and twenty-second days with pain in the right side. Then for seventeen days there was apyrexia, but on the thirty-eighth day the temperature began to rise and signs of consolidation were found. A pleuritic rub was still heard on the fifty-seventh day.

One type, in particular, of delayed convalescence, where the signs (dullness, diminution of air entry, and crepitations) persisted at one base for periods varying from thirty to sixty days, is of interest. These cases were then sent to England,

and there is some evidence that in these men chronic pneumonia, and perhaps chronic bronchiectasis, are, at any rate, occasionally the sequelae.

Toxaemia.

American views. American workers (8) have offered a detailed explanation of this toxaemia in mustard gas poisoning, founded upon an experimental basis. They found that when an animal was exposed to the vapours of mustard in a high concentration, it subsequently showed a complex of symptoms which may be divided into two classes.

(1) Local effects, due to contact of mustard with the tissues of the body, e. g. conjunctivitis, tracheitis, burns, &c. These effects are well recognized.

(2) Systemic effects, due to the absorption of the substance into the blood stream, and its distribution to the various tissues of the body. These effects are not generally recognized.

In order to become familiar with the systemic effects, animals (principally dogs) were given subcutaneous and in other dogs intravenous injections (solution of mustard in water 1 per cent.). Both methods of injecting the mustard produced effects that were 'quite characteristic and unmistakable' on the (*a*) heart, (*b*) alimentary tract, (*c*) central nervous system. Most of these effects have been obtained by the application of large amounts to the skin. Every one of these effects (except the rapid respirations), obtained by injection of mustard, were noted in dogs gassed with very high concentration of gas sufficient by inhalation to kill them in less than twenty-four hours. This work made it clear that the same effects were produced, either by subcutaneous or intravenous injection of mustard or by inhalation of strong concentrations, and that in these high concentrations dichlorethyl sulphide is absorbed through the lungs and produces its characteristic effects upon the body.

The absorption of mustard received further experimental support. Their workers found that the aqueous solution of mustard gas rapidly hydrolyses when in contact with water, breaking up into hydrochloric acid and a body, probably dihydroxyethyl sulphide, which can be detected by converting it back into mustard. When mustard is absorbed by the body it must be mostly or entirely in aqueous solution, and therefore it will in the course of a few hours hydrolyse, unless there is something to prevent it.

The proof that mustard gas is hydrolysed in the animal body was furnished by detecting one of the products of hydrolysis in the urine. When mustard is inhaled in high concentrations, it is absorbed through the lungs, hydrolysed in the body, and the hydrolytic product is excreted in the urine.

They concluded that the probable effects of mustard are due to one of the products of hydrolysis, because the time taken for the solution to hydrolyse *in vitro* is practically the same as the time taken for effects of mustard to develop when injected, and because the absence of any immediate effect when mustard is injected makes this assumption almost imperative.

Which of the products of hydrolysis is responsible for effects of mustard? The objections to the theory that hydrochloric acid is at the bottom of mustard symptoms are considered, and the conclusion is reached that 'although the evidence is not conclusive, such as there is supports the theory that the effects of mustard gas are due to the hydrolysis of the sulphide within the cells and the liberation there of hydrochloric acid'.

French views. The idea of a general poisoning of the system runs through the French literature. A severe case, they argue, is always accompanied by grave general phenomena; these general symptoms sometimes fill up the picture, the local lesions dropping into the background; the fever long persistent is usually higher than the local lesions can explain. In support of these views, they maintain that the renal epithelium rarely escapes damage in serious cases, and, finally, they separate mustard casualties of a grave nature into two groups:

(*a*) The respiratory type.

(*b*) The adynamic type.

The latter they associate with profound impairment of the general health, with signs of severe intoxication of the nervous system, recalling the toxaemia of severe burns, and with hyperpyrexia. Apart from extensive burns, which have become septic, we did not meet with this group. Reference will be made to these views under the various systems. Such a conception of mustard poisoning differs radically from that here set forth, and it is on occasion, as in their remarks on the implication of the kidney, in open conflict with the facts as we found them.

If we reflect on the part played in mustard gassing by the secondary infections of the respiratory system, we shall be very willing to admit that some degree of toxaemia is as common as they allege—is, indeed, rarely absent in a case of any severity. But there is nothing in the facts in our possession to lead us to ascribe this toxaemia to other than bacterial causes. Had circumstances permitted, it appears probable that the toxic types of mustard poisoning could have been classified according to the causal organisms.

Clinical Evidence of Toxaemia.

There are three groups:

(1) *A state of somnolence associated with extensive and septic burns.* One patient stated on the eleventh day that he 'felt quite wide awake and suddenly went off to sleep'; another declared on the nineteenth day that he had 'felt fine the last few days', previously he was 'always sleepy'. In some the condition is more pronounced and may be accompanied by incontinence and by signs of profound toxaemia. It was only found with sepsis: burns, however extensive, which had been treated as wounds from the outset and kept clean were not complicated with this evidence of toxic absorption. It is a true bacterial toxaemia.

(2) *A condition of apathy,* singularly characteristic of mustard gas poisoning. 'The patient has gradually sunk into a lethargic condition; he retains sputum

in the mouth and throat unless encouraged to spit; he takes no interest in his surroundings; has no desire for food.' Note on the eighth day of a case of broncho-pneumonia: the temperature fell on the tenth day.

From the notes of another case of broncho-pneumonia this entry on the tenth day of illness is taken—'Lies still for hours, taking no note of anything; when he coughs Sister goes to him at once or he would not spit out at all: sputum collects even on his lips.' Yet these patients were perfectly rational when roused: there was no wandering, no attempts to get out of bed, no incontinence. Is it not possible that in this condition we have no more than a difficulty in the respiratory exchanges, with consequent anoxaemia and so cerebral anaemia?

(3) *A terminal toxaemia.* This is only seen in fatal cases, and in them is confined to the last two or three days of the illness. Wandering, getting out of bed, and, in some, picking at the bedclothes, or incontinence of urine and faeces, are terminal phenomena which might occur with any fatal infection. The appearance of toxic symptoms in any of the three groups was of little assistance in prognosis and diagnosis. Neither apathy nor somnolence associated with burns was a guide to the subsequent period of invalidism. They were confined to the graver types of mustard lesions, but in some cases, where such symptoms were marked and the illness severe in type, convalescence was much more rapid than in others with an initial lesion apparently of less severity. Nor did the appearance of toxic symptoms in group 3 help in prognosis. When they were noted it was already apparent on other grounds that the end was near. In diagnosis there is the same story: occasionally the advent of signs of toxaemia gave warning of necrotic changes in broncho-pneumonia patches or of actual abscess formation, as in the case quoted elsewhere, in whom wandering at night in the course of an apparently satisfactory broncho-pneumonia phase was the first warning of an abscess which three days later burst into the pleural cavity leading to a pneumothorax. In another fatal case, with death on the fourth day after gassing, many breaking-down necrotic broncho-pneumonia patches were found post mortem. There was a noisy delirium with incontinence of urine and faeces for two days before death, so that in the presence of signs of consolidation necrotic changes were probable. This was the only example in our series of a group described by French writers in whom mental excitement was a marked feature. The patient in question resisted treatment furiously and appeared to be labouring under great mental excitement.

A review of these clinical facts leaves little that cannot be perfectly well put down to bacterial toxins. The toxaemia, even in fatal cases, was not by any means constant. Quite 50 per cent. of our cases which came to post-mortem were perfectly rational, vigorous, and clear-headed until within a few hours of death.

The facts set forth under albuminuria point in the same direction. The only cases in which nephritis was found post mortem had severe septic burns, and in the case of extensive burns it is worth noting that albuminuria did not appear to any extent until widespread bacterial infection had taken place.

Albuminuria in our experience was always associated with profound bacterial infection.

The American work has established that under the conditions of their experiments mustard has a systemic as well as a local effect. But in the concentrations which it is possible to employ in the field there seems doubt whether we have to look farther for an explanation of the signs and symptoms than to the secondary infections which attack the injured parts. It is well to remember that the clinical picture seen in man in no way resembles the symptoms produced by the experiments on dogs. The effects, cardiac, alimentary, and nervous, that result from injection or inhalation in high concentrations are apparently not reproduced in the conditions under which man is gassed. It is, moreover, improbable that a chemical poison had escaped elimination and was still at work upon the tissues when these signs of toxaemia appear a week after gassing. We conclude that the toxaemia is bacterial.

The toxic symptoms hitherto described form part of the picture of the febrile phase of the illness. A chronic toxaemia was supposed by some medical officers to be present in some cases of protracted convalescence. Certainly a curious condition was met with in a small proportion of the graver cases that recovered, and was commonly first noticed in early convalescence. It was an intractable and baffling condition for which it is difficult to find an explanation. The man was like a faltering convalescent from a very grave illness. He seemed to have lost all vigour and pride of limb. He was anxious to lie in bed as long as possible and was unwilling to be disturbed at any time. He had no interest in food and exercise. He was not hypochondriac, and, as often as not, declared himself to be quite comfortable and happy. But he was unfit; had no energy, no vital force; his after-history was unsatisfactory; his resistance to intercurrent disease was definitely lowered.

Such a condition is perhaps due to some obscure form of chronic toxaemia. It is possible, but it is not proven. We cannot even affirm that the after-history of this group is definitely less favourable than that of other mustard casualties without further evidence, though, as stated in our cases, it appeared to be the rule.

In this connexion it is interesting to consider the resistance of mustard gas casualties taken as a group to intercurrent disease.

Liability to Intercurrent Disease after Gassing.

In seventy-five cases in the whole series (4·5 per cent.) the original symptoms of gassing were subsequently overshadowed by the development of a new disease.

(*a*) Influenza. In the course of an epidemic it was found that the incidence of influenza was no commoner in gas wards than in the other medical wards, and that the mortality from influenzal pneumonia was no greater among gassed men than among non-gassed men.

(*b*) Common colds. The same remarks apply to the liability to common colds.

(*c*) Diphtheria. A small epidemic at No. 7 Stationary Hospital had its origin in several cases of sore throat among nurses who did not report sick. Cultures were made from the throats of all the patients in a number of the medical wards. The incidence of carriers among the convalescents from gassing was much higher than among other convalescents, and the positive cultures were found chiefly in the gassed wards. Similar observations have been published (9). The incidence of intercurrent disease is no higher, therefore, than in other hospitals not acting as gas centres or in hospitals at an earlier date, when gassed patients were only present in small numbers.

Period of Invalidism.

Since in mustard poisoning the mortality is only about 2 per cent., the efficiency of the gas as a weapon of warfare must depend on the number of men gassed, and on the average length of time a man is incapacitated. We may consider this period of invalidism under two groups:

(1) Gassed men who never left France but were returned to duty through convalescent camps.

(2) The graver types of casualty who were sent to England as stretcher cases.

1. Records were kept of the numbers discharged to convalescent camps, week by week, with the object of curtailing the period between gassing and discharge. The figures given deal with the disposal of 559 cases admitted during a period of five weeks. Only 2 per cent. were evacuated to England; 1 per cent. died; the remainder were detained till they were able to march to a convalescent camp. In 97 per cent., therefore, we ascertained by the crucial test of experience the precise period that elapsed before each individual could march half a mile in his equipment. 87 per cent. of all admissions successfully passed that test within a month of gassing (57·5 per cent. within fourteen days and 15·5 per cent. within twenty-one days). Taking a month as the maximum time it is possible to keep cases at a French base, we arrived at 13 per cent. as the proportion of all mustard casualties arriving at the Base that it is necessary to send to England.

Bearing in mind that some of the less seriously gassed men do not reach the Base, but are retained in casualty clearing stations and corps gas stations, the fact that 87 per cent. of all who arrive at the Base can march within a month is a partial answer to the question of the efficiency of mustard gas in war.

2. In this group, which we estimate at 13 per cent. of all mustard gas casualties, our investigation has not the same value. It is difficult to keep in touch with the men who have been discharged as permanently unfit, and in those who were eventually returned to duty the period appeared to depend more upon the efficiency of the hospital concerned than upon the lesion.

Reviewing a considerable number of after-histories that we obtained by letter and by the courtesy of the Medical Research Committee, it was found that the period of invalidism varied between three and six months. After six months

the men had either returned to duty or had been discharged as permanently unfit and lost sight of. It was further found that those whose condition was grave while in France were on the whole not detained in hospitals in England as long as those who had given us less anxiety. We ascribed this to the tendency of functional disorders to pass over men with grave organic lesions in favour of a milder type of casualty, just as shell-shock neglects the wounded man.

The Sequelae of Mustard Gas.

In the first three months of 1919 one of us had an opportunity of pursuing this inquiry farther, and of examining in England a number of men who had been gassed many months previously. They fell naturally into three groups:

(1) Men with functional disorders and without signs of organic lesions.

(2) Men under treatment for the 'effort syndrome'.

(3) Men with symptoms and signs pointing to a lesion of the respiratory tract.

It was clear that members of the first group only required treatment under suitable conditions to be restored to health. In one case of functional aphonia of more than a year's duration there was no sign of organic disease on laryngoscopic examination, and the man appealed to his medical officer for the battery which he had seen used in France with happy results in the case of others. The second group is discussed under the 'Effort Syndrome'. In the third group there were some features of interest.

(*a*) *Emphysema.* Dr. Ryle has pointed out to one of us that in a few of these patients apical bulging can be demonstrated if the fingers are placed in the supra-clavicular fossa and the patient is asked to cough, pointing to emphysema in that very region where more than fifty years ago Sir William Jenner was wont to teach the earliest signs of emphysema appear. But it is not possible to say whether this was present before-gassing.

(*b*) A small number were suspected of phthisis; with great emaciation, with cough and muco-purulent sputum, with slight haemoptysis, and with long-continued evening pyrexia, it was a natural sequel to keep in mind, but repeated examination of the sputum for tubercle bacilli, the X-ray examination of the chest, and the subsequent after-history led to a favourable prognosis. This characteristic group is known to all who work among the late sequelae of gas, and an interesting account is given by M. Achard in his communication to the Academy of Medicine (1). He has found that the fever subsides in time, though it persisted for nine months in one case, that the signs clear up, and that the patient eventually recovers completely.

His view that phthisis is no more than a curiosity as a secondary complication after gassing is in agreement with our experience. We have seen but one example in our series, a case with haemoptysis three days after gassing, in whom at the end of a week tubercle bacilli were found in the sputum. This man had been perfectly fit till he was gassed. M. Achard points out that there must

be many with latent tubercle in the army, yet it is infinitely rare to find the disease light up after gassing. He brings forward experimental support of his conclusion that gas does not create in the lung a soil particularly favourable to the growth of the tubercle bacillus. In an officer known to one of us an empyema developed some months after gassing and ended in his death. He had ascribed this empyema to a chill contracted while he was waiting to be boarded as a result of his gassing.

Chronic bronchitis. The gas appears to induce in some men, previously healthy, a condition very similar to that of the chronic bronchitis patient. Further information is needed on this point; we would like to learn if the bronchial mucous membrane remains sensitive to the stimuli of cold and dust, or recovers its indifference to them. The Pension Boards may be able eventually to settle the point when men come before them for reassessment, for they will discover how many days a man was absent from his work in a year, and the medical reasons for his absence.

Chronic pneumonia and fibrosis. Does pulmonary fibrosis occur after gassing, and in that event is it recognizable as the clinical condition to which the name fibroid lung has been given? That it occurs there is no doubt whatever, but we know little of the frequency with which an accurate diagnosis of fibroid lung can be made.

Much has been heard of the evidence of fibrosis in X rays, but those who have most experience of this branch speak with the least assurance. Our own evidence on this point is inconclusive. We shall be content to record the case of a man who died on the fiftieth day: it explains very clearly what is the pathological basis of these late secondary infections which are not uncommon in grave cases.

Case VI. Admitted to No. 7 Stationary Hospital on the second day after gassing: he died on the fiftieth day. The sequence of events can be followed on Chart V.

For the first twelve days the course of the illness was like any other case of severe mustard poisoning. Signs of bronchitis were heard over the whole chest, and this condition of the tubes continued throughout the illness, but the air entry was diminished at both bases, where the percussion note was dull.

From the twelfth to the twentieth days there was a satisfactory improvement in the patient's condition, and this was reflected on the chart: the temperature fell, the pulse was in the eighties, the respiration in the twenties, but the bronchitic signs did not clear up, and on the fourteenth day there were more than two pints of sputum in the twenty-four hours.

On the twentieth day the cough became more troublesome, the dyspnoea more obvious. Three days later it was clear that he was not so well. A hectic flush had come to the face: temperature, pulse, and respiration were rising, and he complained of sharp pain in his right side. On the twenty-eighth day a pleuritic rub was heard near the right nipple, and a fresh patch of solid lung was noted at the right base. On the thirty-third day pleurisy was detected in the left axilla.

The *Bacillus influenzae* was found in the direct cultures of the sputum on the thirty-sixth day and also on the thirty-eighth day, with the addition on that day of *Streptococcus haemolyticus* and a non-haemolytic streptococcus.

There was no sign of improvement, the dyspnoea became more distressing,

the patch of consolidation at the right base spread, and on the forty-eighth day there was again very sharp pain in the left side.

On the day before death ½ c.c. of an emulsion of the sputum in normal saline was injected subcutaneously into the abdominal wall of a white mouse. The mouse died in forty-one hours.

There was an abscess in the site of inoculation: no peritonitis, no pleurisy, no abnormal lung condition. The abscess and the heart's blood both gave on culture a haemolytic streptococcus.

The bacteriological evidence was completed at the post-mortem by the recovery from the lungs, bronchi, and trachea of a *Streptococcus haemolyticus* and the *Bacillus influenzae*.

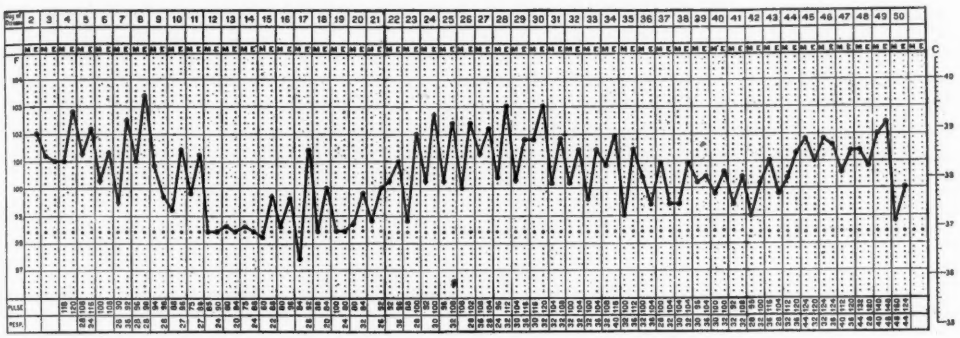


CHART V.

An initial broncho-pneumonia lasting twelve days was followed by eight days of general improvement. But on the twenty-third day a secondary infection had led to a fresh consolidation, the face became flushed, the breathing distressed and hampered by the pain of pleurisy. The report on the sections also shows the sequence of events.

Post-mortem examination. Both lungs were bound down by old and recent adhesions and covered with thick exudate organized in parts. Capt. Shaw Dunn reports on sections made by Capt. Ingram as follows:

'The lesions are of two different dates:

'(1) *Acute.*

'A broncho-pneumonia, in places severe and suppurative, elsewhere fibrinous and catarrhal: also much oedema.

'(2) *Chronic.*

'This is confined to one lobe apparently. The bulk of the alveolar walls are of normal thinness, but in this lobe they exhibit general fibrous thickening. There are also plugs of organizing fibrous tissue in some alveolar spaces, and some of the small bronchioles show very beautifully a condition of "obliterative bronchiolitis". There is also much overgrowth of interlobular fibrous tissue. From its lobular distribution there is no doubt that this chronic pneumonia is the sequel of a broncho-pneumonia.'

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OBSERVATIONS ON SEGMENTAL HYPERALGESIA IN VISCERAL LESIONS

By D. W. CARMALT JONES

With Plates 5–7

Before carrying out any series of investigations upon principles already established it is the usual, and obviously the correct, practice to make oneself familiar with the pioneer work on the subject, and any publication of such investigations is expected to contain a summary of previous writings. When one is working at home, with access to the libraries, the neglect of this is regarded as slovenliness, if not impertinence, but when one has been working abroad under the conditions of the late campaign, the omission may perhaps be pardonable.

So much apology is at any rate due for the publication of a series of observations on so old a subject as the relations of segmental hyperalgesia and visceral lesions without full reference to the classical work of Thorburn, Ross, Head, and Mackenzie, and the reasons for the omission are as follows. I was familiar, chiefly through an association with Sir James Mackenzie, with the fact that a relationship exists between disease of internal organs and increased sensibility of corresponding areas of the skin, and I had made a few desultory observations on the subject in the past. For the first three and a half years of the war, however, I was engaged in duties where there was little opportunity for investigations of the kind, until in March, 1918, I took over charge of the Medical Division of a Base Hospital in France. Where a continuous stream of patients from army areas has to be accommodated, the conditions of work are unsuited to the study of the complete course of any disease, but since the hospitals are large and their occupants constantly changing, a great quantity of clinical material is available for the investigation of any single symptom or physical sign. I made notes on the examination of the skin in about a thousand cases of various forms of disease, and the results point to certain conclusions which I have here set out.

The standard works on Medicine and Surgery were accessible to medical officers at the Boulogne Base, thanks to the energy of the consultants and the

generosity of the Red Cross Society and the Order of St. John of Jerusalem, but the medical journals of past years were naturally not to be had, and it was my intention to consult those bearing on this subject when I was on leave. I found, however, that the previous publications thereon, though not voluminous, contained so much material for thought that I could not do justice to them within the short period at my disposal. Further, it became at once evident that if I had been familiar with them I should have proceeded otherwise than I did in my observations, and also that if I embodied this work in my account I must entirely recast my paper.

However, since the only value of my work lies in the fact that it consists of independent observations and that they cover a considerable amount of ground, I have ventured to put them together in the hope that they may be regarded as an exercise in the principles laid down by the observers I have mentioned.

1. *Principles and Practice.*

Every typical segment of the brain and spinal cord possesses on each side wo sets of fibres—an afferent and efferent somatic, and an afferent and efferent splanchnic. The afferent somatic fibres convey impulses from the skin, and doubtless also from muscles and joints, and impulses to appropriate action are sent down the somatic efferent nerves to the skeletal muscles. The afferent impulses are, or may be, consciously felt, and the action taken is, or may be, voluntary.

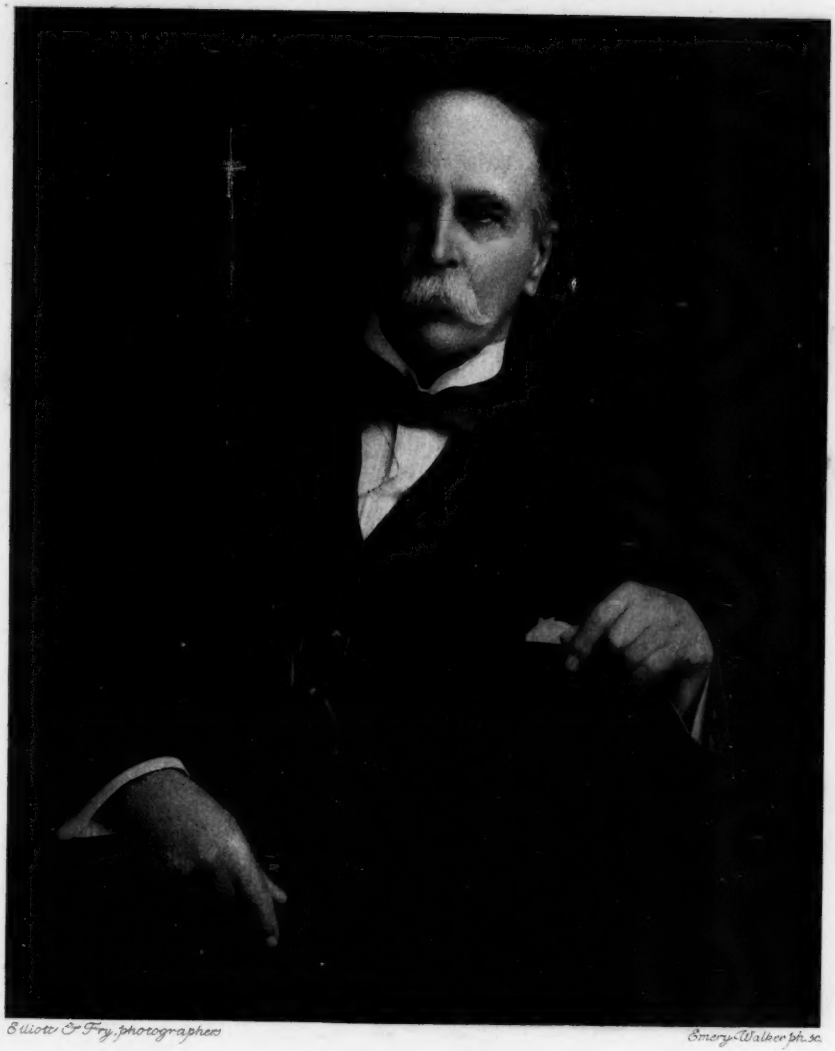
The afferent splanchnic nerves convey impulses from the viscera, and impulses are carried down the efferent splanchnic nerves which induce movement in the visceral muscles, and it may be assumed that the movements are made in response to the impulses transmitted by the afferent nerves. The splanchnic arrangement differs from the somatic in the facts that the splanchnic afferent impulses are not realized in consciousness, and the action taken is involuntary; the state of a viscus cannot be realized from any conscious sensation nor can contraction of any visceral muscle be started or controlled at will. From this it follows that the viscera are not sensitive as the skin is sensitive, and it is stated that if the viscera are exposed by operation without an anaesthetic, they can be handled without the patient being aware that they are being touched. Further, visceral pain is not felt in the organ itself but in the distribution of the corresponding somatic afferent nerve.

In the event of a viscus being *inflamed* the impulses passing up the afferent splanchnic nerves are abnormal, and they induce a state of hyperexcitability throughout the segment to which they belong, with the apparent result that the afferent somatic nerves of the part are rendered more sensitive. The effect of this is that a sensation such as that produced by a light pin-prick, which is not regarded as painful over the general surface of the body, is resented as causing

IN

MEMORIAM

SIR WILLIAM OSLER



Elliott & Fry, photographers

Emery Walker ph. sc.

W. Osler

1907–1919

With the passing of Sir William Osler, on December 29, 1919, this Journal loses its Senior Editor and one of its founders. During the twelve and a half years of its existence he has been indefatigable in encouraging its growth, shaping its policy, and smoothing out its difficulties.

At the time of his arrival in England, in 1905, some physicians in this country wishing to start a Journal on the present lines, recognized how great would be the value of his support, and approached him on the subject. At a preliminary meeting Osler suggested the formation of an Association of Physicians of Great Britain and Ireland, and as a result of this meeting both the Association and the Journal were founded.

As a delegate of the Clarendon Press Sir William Osler was instrumental in securing its assistance in the publication of the Journal, and the Editors gratefully acknowledge the far-sighted and liberal aid of the late Mr. Charles Cannan, Secretary to the Delegates, which has contributed so greatly to its success.

Under a deep sense of personal loss, the surviving Editors, all of whom have been associated with Osler from the foundation of the Journal, feel that in thus setting forth the debt which this Journal owes to him, they add one more to his many claims to grateful remembrance by all who have at heart the progress of medicine.

positive pain when applied to the area of the skin supplied by the same segment as an inflamed viscus.

In other words, inflammation of any viscus induces a state of hyperalgesia in the skin supplied by the same segments of the spinal cord as the viscus. If this is true, it follows that if the nerve supply of the viscera is known, it is possible to diagnose inflammation in any viscus by demonstrating hyperalgesia in the corresponding area of skin. This is the working hypothesis which has been adopted in devising and interpreting the experiments to be described.

The method of investigation is as follows. The only site examined is the surface of the skin, superficial stimulus only being applied. Referred pains, pain on deep pressure, and pain or tenderness felt in muscles are not considered. The only sensation studied is that of pain excited by pricking; the sensations of touch, heat, and cold have not been investigated. The pain is excited by means of an ordinary pin-point; at first a sharpened wooden match was used, but this was afterwards given up, as not giving a constant stimulus. The pin is held between the thumb and index finger, so that the point is on a level with the tips of the third, fourth, and fifth fingers, and when the pin-point touches the patient's skin, these finger-tips touch it at the same time; in this way uniformity of pressure with the pin can be maintained.

The usual method of procedure in any given case is by way of exclusion. It is desired to know whether there is evidence of inflammation of any given viscus. Is the heart inflamed, or is the stomach inflamed? The heart area and the stomach area being approximately known, start pricking at a point well above the suspected area. Use gentle pricks and ask the patient if he feels them. Be careful to use pricks which do not cause him to flinch with pain. Say 'Do you feel this pin-point?' and when answered in the affirmative say, 'Tell me if it changes, if it becomes sharper or blunter?' Then make a series of pricks along a line which crosses a large number of segmental areas at right angles, say from the middle of the clavicle vertically downwards. In a sensitive case the patient will flinch when the pin passes on to the area of skin supplied from the same segment as an affected viscus. Stop the investigation, mark the spot with a skin-pencil, and repeat the experiment from below upwards, say from below the umbilicus, marking the skin again when the flinch occurs. Some patients do not flinch, but will speak of an increased sensation of sharpness. Move laterally from the original line and repeat; in satisfactory cases complete girdles involving one or more segments can be clearly demonstrated. Further, in cases where groups of three or four segments are involved, such as cardiac cases, *the dividing line* between the different segments can be shown to be hyperalgesic: the whole area is over-sensitive as compared with the general skin, but the *edges* of each of the component segments are especially so.

The results to be described were obtained by this method alone: they indicate segmental areas, so far as these are to be distinguished from root areas.

2. *The Area supplied by each Segment of the Brain and Cord.*

It is evident that any one who wishes to establish a relationship between internal viscera and external areas of skin must determine for himself what he is going to regard as the distribution of each segment: he will not find it satisfactory to rely upon the opinions of others, and is compelled to construct his own map.

I have attempted to do this, using elementary anatomical knowledge supported by a map published by Col. Webb-Johnson, D.S.O., A.M.S., in a paper entitled 'The Principles underlying the Distribution of Nerves to the Limb'.[1] This scheme, which is based largely on the views of Ross of Manchester (*Brain*, vol. x, 1887–8), was adopted because it seeks to establish general principles of distribution rather than to indicate the precise limits of any given area. The principle is that if the limbs are placed in the embryonic position, each successive area of distribution will be found from above downwards in numerical order. The arrangement of the areas as indicated by the method of investigation just described conforms very closely to this plan.

With this general scheme in mind, individual areas were worked out in a reciprocal manner. Certain regions of skin were found to be hyperalgesic in heart lesions, and the presence of specially sensitive edges indicated that three or four segmental areas were involved. Others were found in gastritis, others in enteritis, and so on, and in course of time areas were defined which included between them the whole surface of the body, and these were numbered in accordance with elementary anatomy.

The area of distribution which I have mapped for each segment is as follows:

Fifth Cranial nerve. First division. (Fig. 1.) The area is bounded by two lines, one sagittal, starting upon the antihelix of the auricle and passing vertically upwards and across the skull, the other roughly horizontal, passing across the face, below the orbit on to the bridge of the nose about half an inch below its origin from the skull.

Second division. This area is a band which passes across the face from the forepart of the ear to the bridge of the nose. Its upper border follows the lower border of the area of the first division, its posterior border is short and covers a small part of the antihelix and curves into the lower border, which is convex downwards and sweeps on to the nose just above the lower edge of the nostril (Fig. 2).

Third division. This area is a band, roughly triangular in shape, which passes from the forepart of the ear across the lower part of the face and involves the nostrils, mouth, and chin. Its upper border corresponds to the lower border of the second division, its apex includes the tragus, and its lower border follows fairly closely the lower edge of the horizontal ramus of the jaw,

[1] Archives of the Middlesex Hospital.

but there is often an upward bend in the curve which excludes a portion of skin near the angle of the jaw. This is the usual arrangement: it will be seen that there is fairly close correspondence between the three photographs (Figs. 1, 2, and 3), which are taken respectively from a case of rhinitis, a case of otitis media, and a case of parotitis: minor differences have been met with, but the description in the text is that usually found.

Second cervical area. The next area mapped was regarded as being that of the second cervical. Its distribution suggests a 'Balaclava helmet'. It is bounded above by the vertical border of the first division of the fifth cranial, the posterior border of the second division, and the lower border of the third division. Or from the vertex of the skull downwards, crossing the ear and along the lower border of the jaw; its lower border passes round the neck at about the level of the upper border of the thyroid cartilage, and is a little higher behind than in front (Fig. 4 a).

Third cervical area. This resembles a neck-bandage. Its upper edge meets the lower edge of the second cervical at the upper border of the larynx, and its lower edge is at about the level of the cricoid cartilage. It passes horizontally outwards from here so as to involve most of the supraclavicular fossa. It turns back along the upper border of the trapezius, which it crosses to reach the middle line of the back about an inch above the vertebra prominens. This area has been demonstrated both directly, as in Fig. 4, and by exclusion in a patient suffering from diphtheritic tonsillitis, which involved his second cervical area, and from bronchitis, which involved his fourth, the third escaping.

Fourth cervical area. This is something like the trimming round the neck of a vest. It begins behind at the level of the vertebra prominens, which is included in it, and passes outwards to the point of the shoulder; it then turns forwards and inwards and generally covers the clavicle, its lower border nearly reaching the angle of Louis' and the second rib (Figs. 5, 6, 7).

The arm areas, fifth, sixth, seventh, and eighth cervical and first dorsal, are best demonstrated when the arm is held abducted, the forearm extended and the thumb pointing upwards. They can then be demonstrated from above downwards. (See Figs. 6, 7, 8, 9, 10, 11.) The first dorsal has a distribution on the chest wall; the cervicals, from the fifth to the eighth inclusive, are confined to the arm.

Fifth cervical area. This is a strip which passes from the point of the shoulder down the outer aspect of the arm and radial side of the forearm to end at any point between the elbow and the wrist. Figs. 6 and 7 show a frequent distribution.

Sixth cervical area. The sixth cervical area may be mapped immediately below the fifth; its lower border passes along the front of the arm and forearm and palm to the cleft between the index and middle fingers and back along the back of the hand, forearm, and arm to the point of the shoulder.

Seventh cervical area. The lower border of this area is approximately parallel to the preceding and passes along the front of the arm, forearm, and

hand and along the ring finger to its tip, with a similar course along the back of the limb.

Eighth cervical area. Its lower border is roughly parallel to that of the seventh cervical. It ends on the forearm at a variable point between the elbow and the wrist. The area takes in the little finger and ulnar half of the ring finger, and leaves the ulnar border of the arm and forearm to the first dorsal.

First dorsal area. This starts on the back immediately below the fourth cervical; it follows this as far as the shoulder, where it meets the eighth cervical, by the lower border of which it is bounded. It occupies the ulnar border of the arm and forearm, but not the axilla, which belongs to the second dorsal, and it sends a narrow strip along the front of the chest between the fourth cervical and second dorsal, as far as the middle line.

Figs. 6 and 7, showing the fifth and sixth cervicals, are from a case of bronchitis; Figs. 8 and 9, showing the eighth cervical and first dorsal, are from a case of trench fever; and Figs. 10 and 11, showing the fifth and sixth cervical, the eighth cervical and first dorsal, and the seventh cervical by exclusion, are from a case of trench fever complicated by bronchitis.

The distance to which the first dorsal area extends down the forearm is variable; in twenty-seven cases specially noted it was found to reach the elbow seven times, the middle of the forearm six times, and the wrist fourteen times.

The dorsal areas, second to twelfth. These form a series of girdles round the body, which are higher behind than in front; this slope is greater in the lower than in the upper areas.

The second sends a tongue a variable distance down the axilla, generally to a greater extent than that shown in Fig. 12.

The fifth includes the nipple, the sixth includes the ensiform cartilage.

The border separating the ninth and tenth passes through the umbilicus; the border separating the twelfth dorsal and first lumbar passes a short distance above Poupart's ligament and the pubes. There are thus three dorsal areas between the ensiform cartilage and the umbilicus, and three between the umbilicus and the pubes.

The lumbar segments. The lumbar distribution may be compared to a series of aprons united in the middle line behind, in the space between the ribs and sacrum, and united in front just above the pubes, but divided below this so as to form a separate series for each leg (Figs. 21, 22).

The upper border of the first lumbar segment adjoins the lower border of the twelfth dorsal; its lower border starts behind about an inch below the upper and passes forwards and downwards to the front of the thigh, down which it passes for about a third part of the distance from Poupart's ligament to the knee; it then passes inwards and then upwards along the inner aspect of the thigh to the pubes, passing outside the penis, and then turns inwards to meet its fellow of the opposite side. The second lumbar forms a strip below the

preceding which passes two-thirds down the front of the thigh, and whose inner border fuses with that of the first segment in the upper part of the limb. The third, fourth, and fifth form similar strips one below the other; the third reaches to the knee, the fourth to the ankle, and the fifth ends on the dorsum of the foot a little way behind the toes. The lowest points reached by each of these areas is variable, but those shown in Figs. 21 and 22 are often found. The lateral borders of the fifth segment generally cross the external and internal malleoli of the ankle-joint. All the internal borders fuse on the upper and inner aspect of the thigh.

The sacral areas. These cover the buttocks, the perineum, penis, and scrotum, the back of the thigh and leg, the sole of the foot, and the whole of the toes, forming a 'slipper' distribution for the foot. The segmental areas are continued in series with the lumbars. Thus the first sacral starts as a strip below the fifth lumbar and passes down the side of the thigh as far as the knee (Fig. 23); below this point it covers the whole of the back of the calf, the sole of the foot, and the whole of the toes, and passes up the inner aspect of the thigh to fuse with the fifth lumbar near the perineum. The second sacral starts below the first, passes as a strip round the buttock, and below this occupies all the space to the back of the knee. The third sacral forms a ring round the buttocks and passes forward between the legs to include the perineum, penis, and scrotum, meeting the first lumbar just above the pubes.

The fourth sacral is included in the ring made by the third, and itself includes the fifth, which forms a small ring round the anus (Figs. 19, 20, 23).

3. *The Visceral Lesions examined and the Hyperalgesic Areas which were found in each.*

The number of persons examined for the data in this paper were 1,040, of whom 120 were normal men, used as controls. But many of the patients were suffering from more than one disorder, as for instance trench fever and bronchitis, or dysentery and endocarditis, so that more lesions than patients were examined.

On analysing the records I find that I have notes of over a thousand visceral lesions investigated. These are tabulated in the numerical order of the segments involved.

Rhinitis. In many cases suffering from gas-poisoning, acute conjunctivitis and rhinitis were present besides other disorders. Several of these were examined and in six some hyperalgesia was found over the trigeminal distribution. In five it was limited to the first division (Fig. 1), in one all three divisions were involved. These cases were referred to the Consulting Ophthalmic Surgeon, who pointed out that the damage to the eye was of an extremely superficial character and could not be regarded as a visceral lesion.

The condition, however, was clearly demonstrable, and may perhaps be due to the fact that parts of the nose are visceral in origin, and retain the

visceral characteristic of inducing, when inflamed, this referred hyperalgesia in the skin area supplied by the same cranial segment.

Otitis Media. In a similar way inflammation of the middle ear may induce the same change in the area of some division of the fifth cranial nerve. Seven cases were examined and hyperalgesia of the second division was found twice and of the third once. (Fig. 2.)

Parotitis. Seventeen cases of parotitis were examined, of which six were negative and eleven showed involvement of one or more divisions of the fifth cranial nerve: first division, two cases; third division, two cases (Fig. 3); second and third divisions, one case; first, second, and third divisions, six cases. In other words the first division was involved eight times; the second, seven times; and the third, nine times.

Tonsillitis and Pharyngitis. These conditions were examined in thirty-six cases of diphtheria, quinsy, and sore throats of other kinds, with varied results.

Six cases were negative, and among the rest the first division of the fifth was affected once, the third division twice, the second and third once, and the first, second, and third twice: the second cervical area ten times, and the third cervical fourteen times.

In other words the areas affected were: first division of fifth cranial four times, second division three times, third division five times, second cervical area ten times, third cervical fourteen times.

These figures are summarized in Table I.

TABLE I.

	Nose.	Ear.	Parotid.	Tonsil.
V cr. i	5	—	8	4
V cr. ii	1	2	7	3
V cr. iii	1	1	9	5
C. 2	—	—	—	10
C. 3	—	—	—	14

The above figures are of course all small ones and are inserted chiefly to complete the series. Larger numbers of cases have been examined in disorders of most of the other organs.

Respiratory disease. Under this heading are included laryngitis, tracheitis, bronchitis, broncho-pneumonia, pneumonia, and pleurisy. The first cases examined were cases of laryngitis and tracheitis due to poison gas, many of which showed very clearly defined areas of hyperalgesia.

In all, 215 cases with respiratory symptoms were examined, of which 55 gave negative results. In positive cases the cervical areas were the only ones affected. With very rare exceptions the fourth cervical was involved, the fourth and fifth generally, and the fourth, fifth, and sixth frequently: a few of the other cervical areas were occasionally to be made out. The figures were as follows:

Second cervical, 1; third, fourth, and fifth, 1; third, fourth, fifth, and

sixth, 1; fourth, 88; fourth and fifth, 23; fourth, fifth, and sixth, 34; fourth, fifth, sixth, and seventh, 2; fifth, 1; fifth and sixth, 1.

The number of times that each segmental area was involved is set out in Table II.

TABLE II.

Respiratory Disease.

C.	
2	1
3	2
4	147
5	89
6	38
7	1

Cardiac disease. These observations were made on troops, in whom established valvular disease is rare, but disordered action of the heart very common.

The cases quoted here were chiefly examined at a 'heart centre', established at a convalescent camp in France, where most of the men were suffering from the latter condition acquired on service.

A large number, in fact the majority, were found to show hyperalgesia of the seventh dorsal segment, a fact difficult to explain according to the accepted views on the innervation of the heart. I consulted Major H. F. Marris, R.A.M.C., an expert cardiologist, on the point, and he suggested that the condition was due to trench fever, in which he had observed similar bands of hyperalgesia. This observation was followed up, and it was found that in trench fever hyperalgesia was often present in the following segments: 8 c, 1 D.; 7 D.; 1, 2, 3, 4, 5, L. (see Figs. 8, 9, 10, 11, 21, 22). The results obtained in this investigation were published in the *Lancet*, October 5, 1918 ('Sensory Changes in the Diagnosis of Trench Fever').

It was concluded, as a result of these observations, that disordered action of the heart, as seen in France, was in great measure due to trench fever, which is believed to over-stimulate the sympathetic nervous system.

In the present paper it is assumed that cases of D. A. H. which show hyperalgesia of 7 D. alone are due to this infection and are not suffering from any true heart lesion, whereas cases which show hyperalgesia of the upper dorsal nerves are suffering from definite carditis. Some cases showed both conditions. It is only those believed to have true carditis which are considered here.

180 cases were examined; 70 were believed to be due to trench fever alone, 24 had trench fever and a true heart lesion, 54 had heart lesions without trench fever, and 32 were negative. Thus 78 cases showing hyperalgesic evidence of carditis were examined.

Of these, three showed 1 D. alone; thirty-six showed 2, 3, 4, D.; twenty-two showed 2, 3, 4, 5, D.; two showed 3 and 4 D.; ten showed 3, 4, 5, D.; four showed 3, 4, 5, 6, D.; one showed 4 and 5 D.

In 46 cases, therefore, three segments were involved in 26 four segments,

3 showed two segments, and 3 showed one segment. The number of times each segmental area was involved is set out in Table III.

TABLE III.

Carditis.

D.	
1	3
2	58
3	74
4	74
5	36
6	7

Disease of the Digestive Organs. Stomach. Forty-two positive cases of gastritis and of patients suffering from symptoms of gastric dyspepsia were examined, and the following areas found hyperalgesic:

6 D., thrice; 6, 7, 8, D., once; 6, 7, 9, D., once; 6, 7, 8, 9, D., twice; 6 and 9 D., eight times; 7 D., five times; 7 and 9 D., twice; 7, 8, D., once; 7, 8, 9, D., ten times; 7, 8, 9, 10, D., five times; 8, 9, D., once; 9 D., once; 10 D., three times.

Liver. The areas found in jaundice were peculiar, in that they were asymmetrical. Symmetry was the rule in disease of all other organs, but with the liver there were always more segments involved on the right than the left. The results in positive cases were the following:

R. 5, 6, 7, 8, 9, D.; L. 6, 7, D., one case; R. 6, 7, 8, 9, 10, D.; L. 7, 8, D., one case; R. 6, 7, 8, D.; L. 7 D., four cases; R. 7, 8, 9, D.; L. 7 D., one case; R. 7, 8, 9, D.; L. 8, 9, D., one case; R. 7, 8, 9, D.; L. 9 D., two cases; R. 8, 9, D.; L. 9 D., one case; R. 8 D.; L. nil, one case; R. 9 D.; L. nil, one case.

Intestines. 100 cases of enteritis (dysentery, diarrhoea, enteric fever) were examined, of which about 50 were positive. It is usual to find both dorsal and sacral segments hyperalgesic.

10 D. was found forty-eight times, 11 D. six times; the whole sacral distribution was affected twelve times, and some part of it, less than the whole, thirty-two times. The sacrals are involved in increasing frequency from below upwards, the fourth and fifth always, if any, and the condition may spread as far as the third, second, or first. In four cases 11, 12, D.; 1, 2, S. were found.

In cases of appendicitis 10 D. was found five times, 11 D. three times, 1–5 S. twice, S. incomplete twice. The number of times each segment of the dorsal distribution was involved in the various viscera is set out in Table IV. It was not always convenient to examine closely the sacral areas.

TABLE IV.

D.	Stomach.	Liver.	Intestines.
5	—	1	
6	15	6	
7	27	9	
8	20	12	
9	30	6	
10	8	—	53
11	—	—	14
12	—	—	4

Disease of the Genito-Urinary Organs.

Nephritis. Forty-nine cases were examined, 39 positive and 10 negative. All areas were involved between the 9 D. and 1 L. inclusive, but never more than one area of this series in the same patient. 9 D. was affected once, 10 D. four times, 11 D. twenty-eight times, 12 D. five times, 1 L. once. 4 and 5 S. were also found twice.

Seven cases of haematuria were examined; six showed 11 D., one of which also showed 4 and 5 S.: one case was negative.

In the course of routine examination the eleventh dorsal segment was often found hyperalgesic, and the urine then frequently contained albumin; in six instances this was not the case, but oxalates were found. Oxaluria has been far more common among troops in this campaign than it is among civilians at home. In one of these, a hospital orderly, R.A.M.C., who had had several attacks of pain, referred to the right side, there was hyperalgesia of 10, 11, 12, D.; 1 L., R.; and 10, 11, 12, D. L. A case of hydatid of the kidney showed 10, 11, D.; a case of renal colic showed 11 D. and 4, 5, S., and a case of *ren mobilis* showed 11 D.

Cystitis was curiously rare; only two cases were found. One showed hyperalgesia of 1 L. Another was due to a stone in the bladder, which was removed by operation. This case showed 10, 11, 12, D.; 1, 2, 3, L.; 3, 4, S. (Fig. 19 and 20).

Orchitis. Twenty-five cases were examined, 19 positive and 6 negative. Inflammatory lesions of the different parts of the testes are all considered together without attempt at separation. Dorso-lumbar and sacral segments were both affected, generally together, and the results are stated separately.

Dorso-lumbar areas: 10 D., once; 11 D., once; 10, 11, 12, D., four times; 10, 11, 12, D., 1 L., once; 11 D., once; 11, 12, D., four times; 12 D., four times; 12 D., 1 L., once; 1 L., once.

Sacral areas: 4, 5, S., five times; 3, 4, 5, S., four times; 1, 2, 3, 4, 5, S., four times.

The number of times each individual area was found involved in disease of the genito-urinary system is set out in Table V.

TABLE V.

Genito-Urinary Disease.

	Nephritis.	Haematuria.	Oxaluria.	Varia.	Orchitis.
9 D.	1				
10 D.	4	—	1	2	7
11 D.	28	6	6	4	10
12 D.	5	—	1	1	14
1 L.	1	—	1	1	3
1 S.	—	—	—	—	4
2 S.	—	—	—	—	4
3 S.	—	—	—	—	8
4 S.	—	—	—	—	14
5 S.	2	1	—	1	14

One case of acute thyroiditis showed hyperalgesia of D. 1.

4. *Discussion.*

Assuming these observations to be on the whole correct, questions arise of both clinical and physiological interest. The clinical question is how far segmental hyperalgesia is to be regarded as diagnostic of a lesion in a given area. The answer depends on how often the hyperalgesia is found, whether it is constant for a given lesion, and whether it ever occurs in the absence of a lesion. Some evidence is available on these points.

Segmental hyperalgesia is not universally present in visceral disease. Individuals vary extremely in the readiness with which they show it; great variations in force in the use of the pin are necessary with different patients, and many conditions which are not understood influence the matter; there are days when the phenomenon is readily demonstrated in nearly all subjects, and on other days the results are uniformly unsatisfactory. I have not been able to associate this fact with any particular state of the atmosphere. The best results are, however, always obtained at the first examination of any case. The sensations aroused should be quite unexpected, and if the patient gathers that he is expected to flinch at any given point as a piece of demonstration, the value of the experiment is quite vitiated.

I have indicated that negative cases have been frequent among those examined, and the proportion is greater than my figures suggest, because negative cases frequently escape record, from lack of interest. I made one series of 250 consecutive cases, in which pains were taken to record all, whether positive or negative; the results of these were 180 positive, 70 negative—rather more than 2 to 1.

I had the opportunity of showing some of these cases to a consulting surgeon, who remarked on the ease with which the condition was demonstrable, and said that in a large experience in civil practice he was unfamiliar with such a degree of sensibility. It is possible, therefore, that the conditions of active service may render men unusually sensitive. It is to be noted in this connexion that the subjects of trench fever show these areas very readily, that this fever appears to stimulate the sympathetic system, and that the general stress of campaigning appears likewise to stimulate that system, which may be the explanation of the remarkable frequency of this hyperexcitability among troops.

In cases of very acute illness, although symptoms may be marked, hyperalgesia is often not demonstrable, probably because the attention cannot be concentrated. For instance, during a malarial rigor I have never demonstrated hyperalgesia in a fair number of attempts; and in cases of nephritis dangerously ill I have also failed.

I conclude, then, that in the most favourable circumstances, segmental hyperalgesia will not be found in more than three cases out of four, and that it will rarely be found in any case of very acute illness.

When present, what is the value of the phenomenon? This depends on what is found in control cases, and the occurrence of paradoxical cases among

patients. The controls in this series are 120 in number, and the most important of them a group of 109 taken from a draft of young soldiers on disembarkation in France, who had not yet gone on active service.

Of these, fifteen showed hyperalgesia of one segment or another, and three of these were referable to some cause such as diarrhoea, sickness, or colic. Of the remainder, nine showed hyperalgesia of 7 D., two of 10 D., and one of 11 D. One case in twelve, therefore, among healthy youths showed slight but quite demonstrable hyperalgesia without any symptoms of visceral disease.

Among patients the following paradoxical cases were found:

In a cardiac case 11 D. In respiratory cases 7 D., three times; 9 D., twice; 10 D., four times; 1 L., twice. In gastritis 1 L. In cases of fever, without corresponding symptoms, 3, 4, 5, 6, C.; 4 C.; 4 D; 7–10 D.; 1–5 S. In renal disease 7, 8, 9, D.

In all cases showing 11 D. hyperalgesia the urine was examined; in one case, that of a patient apparently well and just about to be discharged, the urine was found full of albumin, and in a day or two oedema and other symptoms of nephritis occurred. Small traces of albumin were often found, and in other cases, as noted above, oxalates, but three cases are recorded in whom the 11 D. was hyperaesthetic with normal urine. I conclude, therefore, that segmental hyperalgesia in the diagnosis of visceral lesions has considerable value in positive cases, but is not infallible, and that its negative value is negligible.

The other points to be considered are chiefly of physiological interest, and derive therefrom any clinical importance which may attach to them. Continuing in the assumption that these observations are accurate, what physiological conclusions can be drawn, or rather what suggestions can be made as to the innervation of the viscera?

One case in particular requires mention, that of a patient suffering from stone in the bladder, who was examined after he had been shaved ready for operation, and whose photograph is shown on Figs. 19 and 20. There was hyperalgesia of 10, 11, 12, D.; 1, 2, 3, L.; and 4, 5, S. The patient was re-examined some weeks later, after the operation, when the wounds were healed, but hyperalgesia still more extensive was found, involving 10, 11, 12, D.; 1, 2, 3, 4, 5, L.; 1, 2, 3, 4, S. From this I conclude that there was an original hyperalgesia due to the lesion, and that the operative interference with the parts caused a spread of this over the adjoining segments.

If this be so, it appears that the central segments of any group should be selected to represent the organ affected, outlying ones being considered as accessory and due to spread on account of some particularly acute inflammation. Referring, therefore, to the results detailed above, I suggest that the innervation of the viscera may be as follows: Lungs, 4, 5, 6, C. Heart, 2, 3, 4, D., or 3, 4, 5, D. Stomach, 7, 8, 9, D. Liver, 7, 8, D. Small intestine, 10 D. Large intestine, 4, 5, S. Kidney, 11 D. Testes, 11 or 12 D.; 4, 5, S.

I suggest here that the heart may be innervated from the second, third, and fourth dorsal segments, or from the third, fourth, and fifth, for in more than half

the cases examined, three segments only were found hyperalgesic. I am informed by embryologists that the thoracic and abdominal viscera are not segmental structures, that is, that there is no evidence that the stomach, for instance, represents three rings of intestinal tube developed respectively from the seventh and eighth and ninth dorsal segments; they are developed independently and receive their innervation later. It is not, therefore, remarkable if slight variations occur in the precise segments which supply particular viscera. I conclude, therefore, that this method of examination can only be counted upon to give approximate information as to the innervation of the viscera, and that the innervation itself is subject to slight variations.

With regard to precise localization of lesions in the intestinal tract there are a few facts to be borne in mind. Among thirty-six cases of tonsillitis and allied conditions all three divisions of the fifth cranial, the second and third cervicals have been found involved, whereas for the whole length of the small intestine only 10 D. seems to undergo hyperalgesia. This paradox of a single small organ, in which the lesion is visible, involving five different segments, and many feet of intestine only involving one, makes it difficult to attach great diagnostic importance to this method for the localizing of lesions. The explanation may, perhaps, be as follows: The chief motor nerve of the small intestine is the vagus, a cranial nerve, but the ileo-caecal valve, or the ileo-colic sphincter, is supplied by the sympathetic, and it appears possible that all sphincters are innervated by the sympathetic. It is difficult to see how any irritation of the afferent fibres of the vagus, a cranial nerve, could be followed by hyperalgesia of the skin supplied by the dorsal nerves, whereas irritation of the afferent fibres of any nerve of the dorsal sympathetic might readily be followed by hyperalgesia in the corresponding somatic distribution. I suggest, therefore, that a condition of inflammation in the intestine will induce disturbance in the sphincters of its own divisions, certainly in that below, and often in that above. In cases of dysentery the 10 D., corresponding probably to the ileo-colic sphincter, was always found involved, together with 4 and 5 S., corresponding to the internal sphincter of the rectum. This was also the case in appendicitis. In cases of enteritis confined to the small intestine one would expect to find 10 D. as before and 9 D. corresponding to the pylorus. In a few cases of gas-poisoning, with frequent vomiting, 6 D. and 9 D. were found, and it is possible that 6 D. corresponds to the cardiac sphincter, the lower end of the oesophagus: this is, of course, little more than a guess. So far as any reliance may be placed on these observations for purposes of diagnosis when operation is required, supposing, for instance, doubt were to arise between a perforated duodenal ulcer and acute appendicitis, it would be wise to determine hyperalgesia of 9 and 10 D. before deciding on the duodenum, and 10 D. + 4, 5 S., before deciding on the appendix.

The presence of hyperalgesia in the sacral areas in cases of nephritis raises the question whether there is anything of a sphincter character at the lower ends of the ureters, and the same in orchitis possibly indicates prostatic inflammation.

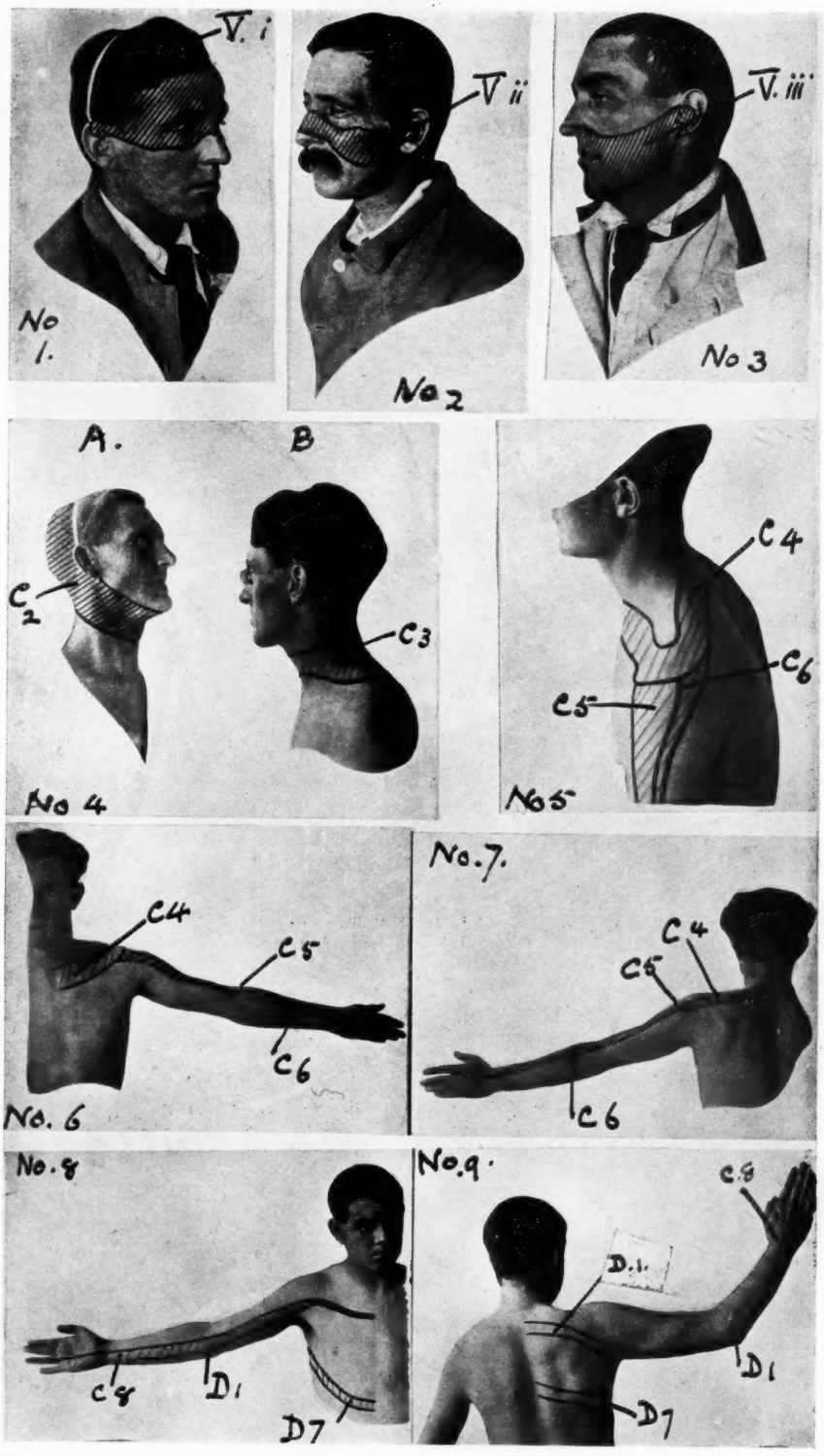
The presence of segmental hyperalgesia is not to be considered as a short cut to the diagnosis of visceral lesions. Its investigation is, however, a source of great clinical interest, and with practice it becomes a distinct adjuvant to diagnosis; it often gives an early clue to an incipient lesion, and there are instances in which it may be of first-rate importance as the determining factor in differential diagnosis.

DESCRIPTION OF FIGURES.

The pictures were prepared as follows: The hyperalgesic borders were determined as described in the text, and painted on the skin with grease-paint. They were then photographed in the department of Captain C. H. Hopwood, R.A.M.C., official medical photographer to the B.E.F. The painted lines were found to be insufficiently definite for purposes of demonstration, so they were artificially darkened on the prints, which were then rephotographed. My sincere thanks are due to Captain Hopwood for the excellence of his work, and for the interest taken by him in the subject and the care expended on the pictures.

Figure.	Segmental area.	Disease.
PLATE 5:		
1	Fifth cranial, first division	Rhinitis
2	Fifth cranial, second division	Otitis media
3	Fifth cranial, second division	Parotitis
4 A	Second cervical	Tonsillitis
4 B	Third cervical	Tonsillitis
5, 6, 7	Fourth, fifth, sixth cervical	Bronchitis
8, 9	Eighth cervical, first dorsal, seventh dorsal	Trench fever
PLATE 6:		
10, 11	Fourth, fifth, sixth, seventh, eighth cervical; first dorsal	Bronchitis and trench fever
12, 13	Second, third, fourth, fifth dorsal	Carditis
14, 15	Seventh, eighth, ninth dorsal	Gastritis
PLATE 7:		
16	Tenth dorsal	Enteritis
17, 18	Eleventh dorsal	Nephritis
19	Tenth, eleventh, twelfth dorsal; first, second, third lumbar	Cystitis (stone in the bladder)
20	Tenth, eleventh, twelfth dorsal; first, second, third lumbar; fourth, fifth sacral	Cystitis (stone in the bladder)
21, 22	First, second, third, fourth, fifth lumbar	Trench fever
23	Tenth dorsal; first, second, third, fourth sacral	Enteritis

Figures 8, 9, 21, 22 were published on a larger scale in the *Lancet* of October 5, 1918, to illustrate the paper above mentioned. I have to acknowledge the kindness of the Editor in allowing me to reproduce them here.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V. iii
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C4
C5
C6
No. 6
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D1
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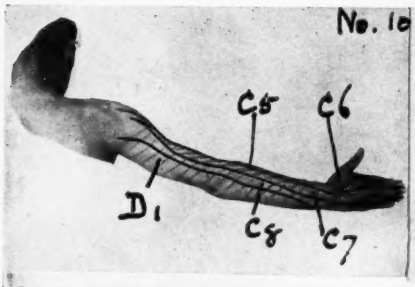
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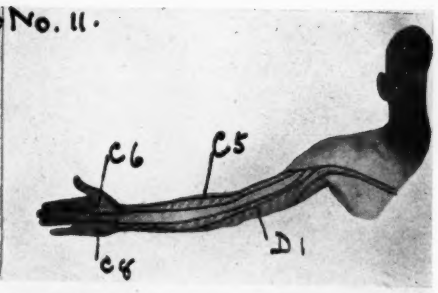
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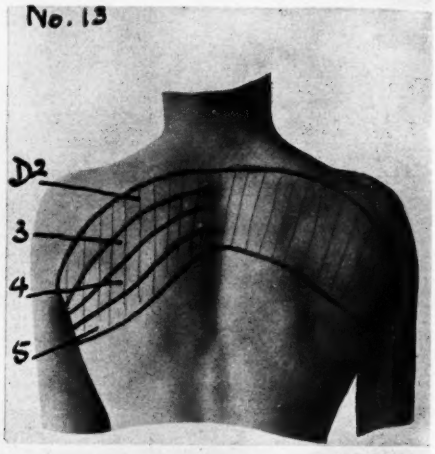
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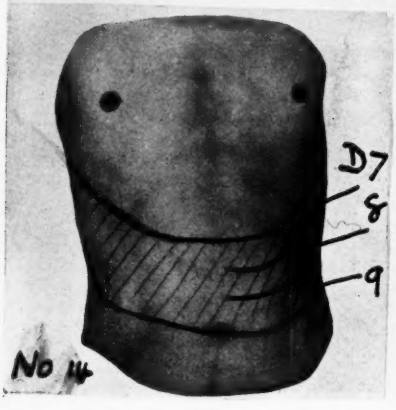
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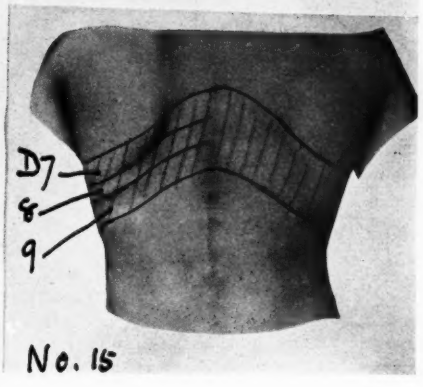
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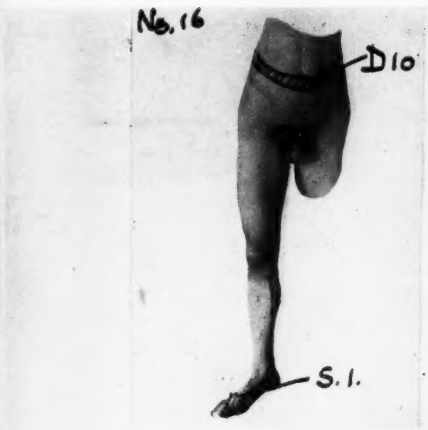
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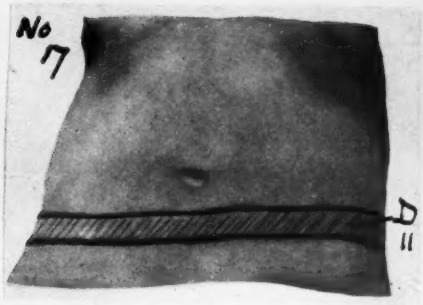
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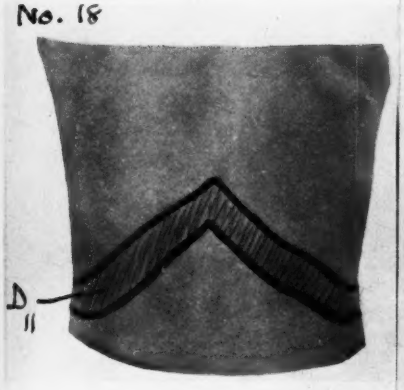
D 11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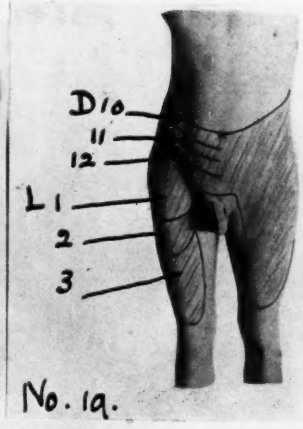
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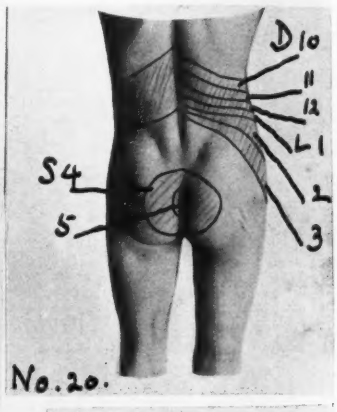
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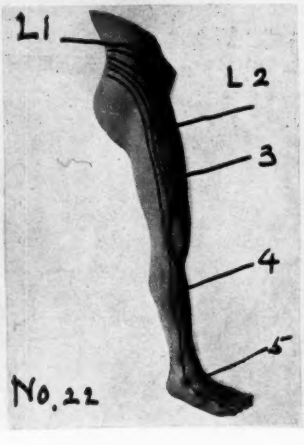
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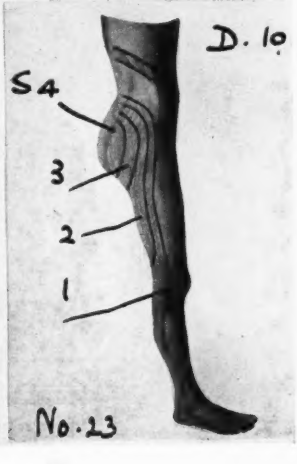

D. 10
S4
3
2
1
No. 23

ANAPHYLAXIS IN THE TREATMENT OF HAEMOPHILIA

By H. W. C. VINES

THE treatment of haemophilia up to the present time has been of necessity palliative or expectant, for hitherto no method has been devised whereby the fundamental cause of the condition can be improved permanently or for a prolonged period.

In the following paragraphs a method of treatment is put forward, not as a specific cure, but rather as suggesting a line of investigation along which further research may be carried out, and it is hoped that from it suggestions may be obtained by which the causation and treatment of other conditions involving similar problems may be indicated. Perhaps the chief interest in this method lies in the use of the anaphylactic state and its phenomena as a therapeutic measure, for hitherto anaphylaxis in man has been regarded rather as a foreshadowing of possible disaster than as a means of benefit. For though much work has been done on the study of anaphylaxis in animals, our knowledge of this condition in man is still very obscure, and it is owing to this lack of knowledge that any forecast as to the duration of the beneficial effects apparently obtained in haemophilics is entirely unreliable.

The two cases recorded here will be discussed in full detail, and an attempt will be made to form a conclusion as to the mode of action of the treatment and, as far as possible, to correlate the phenomena observed with the recorded experimental findings in animals.

Case I. H.-K., male, aged 6 years. The patient was brought to hospital for uncontrolled bleeding from a cut over the right eye. The cut was about an inch long, and in addition there was bruising over the right superior maxilla and a fluid effusion into the left knee-joint. He was admitted to the wards at 2 p.m. on March 14, 1919: at 10 p.m. he was still bleeding, and a dressing of normal horse serum failed to arrest the haemorrhage. At 12.45 a.m. the wound was stitched and a tight bandage applied round the head: in this way the bleeding was controlled by pressure, though the cellular tissue round both eyes became much infiltrated with blood. 10 c.c. of normal horse serum were given subcutaneously and no anaphylactic reaction occurred, either local or general.

On looking up the records, it was found that the child had been attending as an out-patient for haemophilia for a considerable time, and had on several occasions been admitted for uncontrolled bleeding: the following is a synopsis of the previous history:

June, 1917.	Injury to scalp: large haematoma.
Sept. 12, 1917.	Bleeding for five days from a cut lip.
„ 26, „	Several attacks of severe bleeding, very blanched.
May, 1918.	Pain and swelling of right ankle-joint. Admitted with bleeding from the gums. 10 c.c. of normal horse serum given. Transfusion with mother's blood.
June, 1918.	Left elbow painful: haematoma over left internal malleolus: bleeding from the gums for two days: transfusion.
Sept. 1918.	Graze on left temple: small haematoma. Effusion into left knee-joint.
Jan. 1919.	Effusion into left knee-joint: admitted for transfusion: attempt to transfuse was unsuccessful, and continuous bleeding occurred from the incision: 10 c.c. normal horse serum by mouth: coagulation ratio = 4·6.
Feb. 1919.	10 c.c. normal blood injected into buttock: coagulation ratio = 4·6.

The chief points of interest in this history are the frequency and multiplicity of haemorrhages and joints affected, and the inadequacy of all forms of treatment, including transfusion, to effect more than a temporary improvement of the condition.

The family history may be given as follows:

♂ = Haemophilic.

Showing that the patient's maternal grandfather and great-uncle were both haemophilics, though according to the mother's statements the intermediate male generation appear to have escaped. The patient's brother is not a haemophilic and presents a normal coagulation time.

In the appended charts is shown the variation of the coagulation time over a prolonged period. Chart I shows the effect of normal horse serum, and Chart II that of normal sheep's serum. The abscissae indicate the dates on which observations were made, and the ordinates show the coagulation ratios. The line drawn from ordinate 1 indicates the normal coagulation ratio. The method used for estimation of the coagulation time was that of Sabrazès and McGowan. The same method was used throughout all the experiments, and at each observation the coagulation time of the same normal individual was observed: the two results were expressed as a ratio, with the normal as denominator. The figure so obtained is termed the coagulation time ratio, and is not an exact measurement, but a comparative one. Throughout the blood was obtained by needle puncture of the ear or finger. Nolf and Herry (1), in their peptone treatment, found a greater change was obtained in blood from a finger prick than by vein puncture. Further, the difficulty in the treatment of haemophilia lies not in the arrest of haemorrhage from relatively large vessels which can be picked up and ligatured, but in controlling capillary oozing.

The first observation made was on the day following admission and after the patient had received 10 c.c. of normal horse serum and 6 c.c. of his mother's serum subcutaneously. The effect of these measures wore off rapidly, and by the fifth day from admission the coagulation time was very markedly delayed. No further haemorrhage occurred from the scalp wound. There then followed a period in which the delay in coagulation became stationary until March 25, ten days after admission.

At 6 a.m. on that day haemorrhage commenced from the wound in the forehead. A hydrogen-peroxide dressing was applied and the tight bandage renewed. At the same time it was thought desirable to give a further injection of horse serum, but as it was now the eleventh day from the previous one, it was thought that the patient might be in the anaphylactic state. An intradermal injection of two minims of horse serum was given as a test, and a strong local reaction occurred showing that the anaphylactic state was present. No further haemorrhage occurred from the wound. Twelve hours after the administration of the intradermal injection, the coagulation time was taken and found to be equal to that of the normal control. During the next twelve days the coagulation rate remained within limits approximately normal: no further haemorrhage occurred and the effusion in the left knee-joint became slowly absorbed, so that movement was no longer painful. On March 31 two stitches were removed from the wound on the forehead. The wound was found to be covered with a thick scab, in which the stitches were firmly fixed, and though their removal caused some bleeding, it was no more in quantity or duration than might occur in a normal individual under similar circumstances. The bandage was replaced, but came off during the night, but no bleeding occurred, and a few days later it was entirely dispensed with.

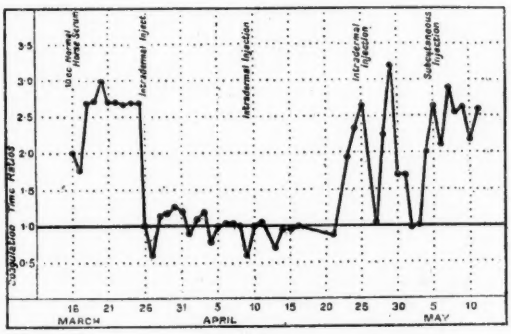


CHART I.

Although the coagulation time remained decreased, a second intradermal injection of the same amount of serum was given on April 10 to see if any further effect would be produced. A similar but less marked reaction was obtained at the injection site, and, six hours after it, the coagulation rate was found to be further depressed. The reaction which occurs under these conditions may be briefly described. The actual injection of the intradermal dose causes the appearance of a small swelling the size of a pea. If the patient is anaphylactic to the protein injected, this swelling rapidly becomes a raised urticarial weal in five to fifteen minutes. The base of the swelling is surrounded by a flushed areola, an inch or more in diameter. In the course of a few hours the outline becomes less distinct, leaving a firm indurated nodule, which has usually disappeared within forty-eight hours after the injection. No marked discomfort is experienced by the patient.

No change occurred in the coagulation rate till April 24, or twenty-nine days after the primary fall. A slight effusion into the left knee-joint was noted on April 23, and on the next day it was found that the coagulation ratio was 1·95. It rose rapidly till on the 26th it reached 2·6. Another similar intradermal injection was given which caused a fall to normal. This, however, did not last, and was succeeded by a higher rise. At this last injection, the reaction obtained was so extremely slight that, in an individual who was not expected to be anaphylactic, it would have been disregarded. As the coagulation time had

again risen very considerably, on May 6 half a minim of serum was given subcutaneously; no effect was produced, either local or general.

From these results there seems to be strong reason for supposing that the patient was no longer anaphylactic to horse serum, and further that the anaphylactic state had commenced to be manifestly decreased on April 23, or one month after its commencement, if the accepted view of an incubation period of eight to ten days is followed. Regarding the short duration of this period a further factor must be considered. The patient had previously had several injections of horse serum, but that he was not anaphylactic to this serum on his admission on March 16 is certain. It seemed possible that his previous injections may have had some effect in reducing the anaphylactic period by the establishment of a partial immunity to this particular type of protein. Therefore, since anaphylaxis is said to be specific to the species of animal protein used, it seemed permissible to sensitize the patient afresh to the serum of another species in the hope that, as he had not been previously sensitized to it, a longer anaphylactic period might be obtained.

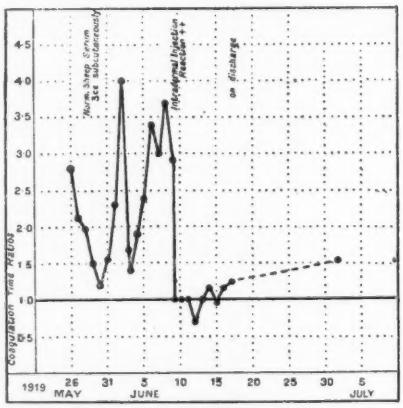


CHART II.

It was, therefore, decided to sensitize him to sheep serum, and though Leary (2) states that this serum is toxic to man, and a local reaction may occur at the injection site, in the present case no such toxicity was apparent. The results of this experiment are given in Chart II.

A sensitizing dose of 3 c.c. of normal sheep serum was given subcutaneously on May 28, after a precautionary intradermal injection had been made on the previous day: there was, however, no reaction to this. The coagulation time fell gradually till May 30, but did not reach the base line. On May 31 it commenced to rise, and on June 2 a very sharp rise occurred, followed by an equally sharp fall on the following day, constituting what might almost be termed 'a haemophilic crisis'. A somewhat similar crisis occurred in Chart I between April 28 and May 1, but it was thought at the time that it might be due to the effect of the intradermal injection of May 26. On the present occasion no joint effusions occurred, and, as the patient had no external lesion of the skin, no haemorrhage took place. The coagulation rate then rose with some rapidity and appeared to be becoming stationary about ordinate 3. On June 9 an intradermal injection of sheep serum was given. A very rapid and very strongly marked local reaction followed. The coagulation time at this period was examined hourly, and the resulting observations are shown in Charts III and IV. Chart IV shows the coagulation time ratio, and Chart III the actual time in minutes over a period of nine hours following the injection. The main point of interest is the rapidity

with which the coagulation time falls. In two hours from the time of injection it became normal. It follows, therefore, that whatever the intrinsic action of the intradermal injection may be, its effect must become very rapidly generalized, for the injection was made into the skin of the right arm, and the blood was obtained for examination from either ear a relatively short time afterwards.

After it had once fallen the coagulation rate remained decreased during the period of hourly observation: no very marked fall below normal was observed. The patient remained perfectly normal throughout, even though the local reaction was a severe one: none of the symptoms of general anaphylactic shock were elicited, and there was no pain at the site of injection, apart from the discomfort of the actual skin puncture.

The coagulation time remained within normal limits up to the time of discharge, eight days after the intradermal injection. During this time, passive movements of the left knee-joint were made, with the object of straightening the limb: no effusion occurred into the joint. The patient was allowed to get up and no untoward results occurred, apart from the fact that he still bruised very easily: such ecchymoses were, however, small, and did not suggest subcutaneous haemorrhage of any extent. They may have been due to the increased fragility of the vascular walls, which some authors claim as a conspicuous symptom in haemophilics.

Case II. F. P., male, aged 17 years. This patient was brought to hospital for uncontrolled bleeding from his lip following a bicycle accident. The bleeding occurred from a cut on the mucous surface of the upper lip on the left side.

His history is as follows:

6 years old.	Knocked down by a tram and hit the back of his head: a large swelling occurred which burst and bled profusely.
8 years old.	Tonsillotomy and removal of adenoids. Profuse bleeding followed the operation.
13 years old.	Bleeding from a cut lip for several days, effusion into the left knee-joint.
8 months ago.	Cut arm which bled profusely and oozed for some weeks.

As regards the present haemorrhage, the patient fell off his bicycle on April 14, 1919, and cut his upper lip severely. The wound was stitched, but oozing occurred intermittently for ten days. The stitches were then removed and the bleeding increased: previous to admission this had been continuing for thirteen days. He had also suffered as long as he could remember from oozing from the gums after using the tooth-brush.

The following genealogical table shows the haemophilic tendency in the present generation: the history of the maternal grandfather and his male relations is unfortunately unobtainable:

♂ = Haemophilic. Pt. = Patient. D. = Died.

From the account given by the patient's mother, all the males of the present generation are haemophilics, except one who is an infant of eight months and whose condition has not yet revealed itself: one child died from haemorrhage. The percentage is remarkably high for an inherited trait, but there is, of course, a possibility of inaccuracy.

The present case was first seen on April 27 and the coagulation time ratio was then 2·25. Attempts were made to stop the bleeding by the usual haemo-

static methods, but these were only temporarily successful: on April 30 he was still bleeding and was admitted to hospital. On complete examination there was found to be an effusion into the left prepatellar bursa, with a purplish discoloration of the skin over it. The patient did not remember having struck his knee at the time of the accident, but had complained of stiffness and swelling in it some hours later. The effusion was probably of a haemorrhagic character, though the joint itself was not affected.

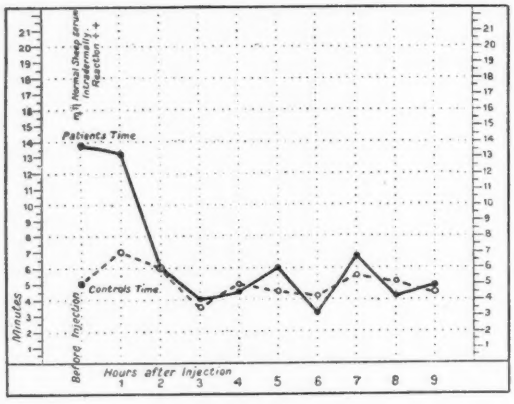


CHART III.

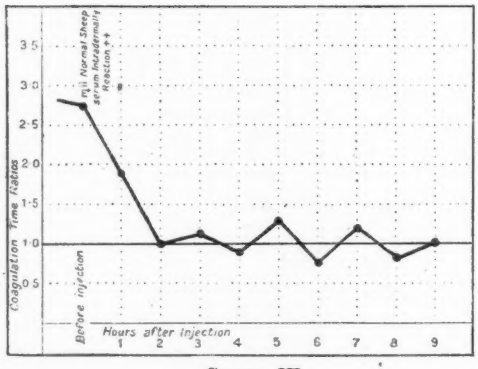


CHART IV.

On admission to hospital the coagulation ratio was found to have fallen to 1·15. On April 30, 10 c.c. of normal horse serum were injected into the subcutaneous tissues, but the bleeding was unaffected, except temporarily. On May 1 the coagulation rate had still further decreased, but on the day following rose again. This fall in coagulation time is therefore seen to occur in both cases immediately following severe or prolonged haemorrhage. It may either be due to a natural protective mechanism, as in normal cases of severe haemorrhage, or it may be connected with the administration of serum. Of the two, the former appears the more probable, and in any case it is of a very transient nature.

For the next ten days following the injection of the primary or sensitizing dose of serum, the coagulation ratio was never below 1·5. The oozing from the lip ceased entirely on the fifth day from admission. On the eleventh day two-fifths of a minim of serum was given intradermally. The coagulation time fell

to normal within twenty-four hours, and though small rises occurred on two occasions, it remained on the lower plane till the time of discharge, eight days later. There was no further haemorrhage from the wound, which healed normally, and though the gums had become very septic from retained blood-clot, no oozing occurred from them. The reaction to the intradermal dose on May 11, when a very minute amount of antigen was given, was delayed: on the day previous to discharge a second dose of two minims of undiluted serum was given, and a rapid and well-marked reaction was provoked.

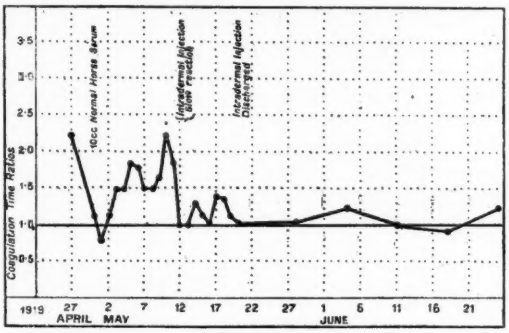


CHART V.

After his discharge, the patient returned to his previous occupation as a packer, and attended weekly to report on his condition. As his coagulation time could therefore only be observed once a week, there is a certain danger of obtaining a false picture if this is taken as the only criterion, for it has been shown (Chart I) that considerable transient falls in time may occur, and should such a fall and the weekly observation coincide, a wrong impression would be obtained. The patient was questioned concerning the occurrence of bleeding, and the following notes made:

May 28. No haemorrhage or joint effusions. Bleeding from the gums on cleaning the teeth still occurs, but now lasts only five minutes as against an hour or more before treatment.

June 4. The bleeding from the gums no longer occurs.

June 11. Six days ago, the pulp of the right thumb was accidentally cut by a knife rather deeply: considerable bleeding immediately followed, but only lasted for ten minutes: it ceased naturally without the application of haemostatics. The patient states that previously such accidents were usually followed by prolonged oozing. No joint effusions. No bleeding from the gums.

June 18. No haemorrhages have occurred, although there are several skin abrasions and scratches on the hands.

In order to control the foregoing observations, it was considered necessary to observe the effect of the intradermal reaction on the blood-coagulation rate of the normal individual when in the anaphylactic state. The processes used were as far as possible identical with those already described: the coagulation rate was observed on successive days at a constant temperature of 20° C.

The normal coagulation rate was determined on two successive days (Chart VI), and then 2 c.c. of normal sheep serum were injected subcutaneously in the left forearm as the sensitizing dose. A slight local reaction occurred at the injection site. There was a diffuse swelling beyond the limits of that caused by the volume of the injection, flushing of the skin, local fever, but no induration

of the tissues: there was no local pain and no general discomfort. The sensitizing dose was followed by a slight acceleration of coagulation rate lasting for forty-eight hours, when it returned to its previous level. On the fourth day after the injection the rate was again accelerated, and for no apparent reason. Four hours after this observation had been made, however, considerable irritation was felt in the area of the primary injection, and it was found that an urticarial rash was appearing. The rash occurred in crops throughout the four following days; each crop lasted for about four hours, and then gradually disappeared: it was accompanied by intense irritation, local oedema, and marked localized heat of the affected area, but no pain. The site of the sensitizing injection was in the upper third of the extensor surface of the left forearm, and it was here that the rash first appeared. The successive crops were on the whole centrifugal as regards the injection site, and twenty-four hours after the first appearance of the rash the affected area extended from half an inch above the elbow-joint to a point $3\frac{1}{2}$ inches above the wrist-joint, covering almost the whole width of the extensor surface but leaving the flexor aspect unaffected. The units of the rash appeared first as small red points, rapidly increasing in size, becoming papular, and finally presenting the typical appearance of an urticarial weal: coalescence then occurred, covering relatively large areas. As regards general symptoms, the temperature in the mouth, twenty-four hours after the rash appeared, was 99·4° F.: there was a feeling of 'slackness', but, apart from the local irritation, no discomfort: there was no tachycardia and no change in respiration rate.

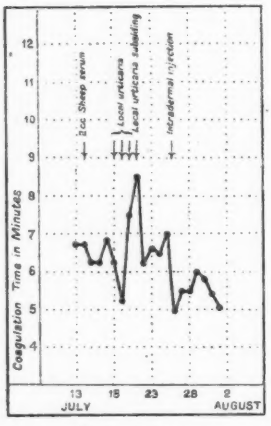


CHART VI.

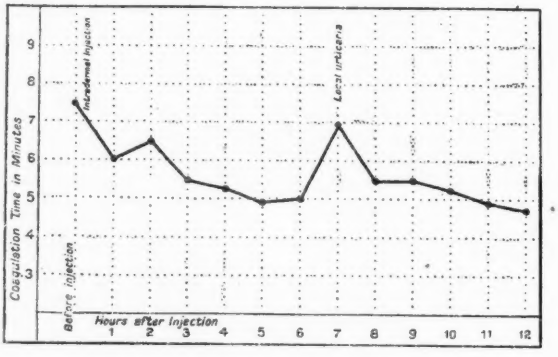


CHART VII.

The axillary and epitrochlear lymph glands of the affected arm were enlarged and palpable but not tender. The coagulation rate at the end of the first twenty-four hours of this 'serum reaction' was markedly accelerated. It is perhaps worth noting that during the course of this reaction to the sensitizing dose all the symptoms were localized with the exception of the slight fever and the changes in the coagulation rate. It may also be noted that in the cases already quoted this serum rash did not appear, and that there were no marked changes in coagulation rate during the period of absorption of the sensitizing injection.

The urticarial attack continued for four days, gradually subsiding: during that period the coagulation rate, which had in the early stages become accelerated, underwent a marked prolongation, returning to the normal on the subsidence of the reaction: this observation is of some interest in view of the diverse findings of Widal (35) and Shattuck (36) in cases of urticaria and serum sickness.

Eleven days after the administration of the sensitizing dose, an intradermal

injection of 0·2 c.c. of sheep serum was given into the skin of the opposite forearm. A well-marked local reaction followed, and the coagulation rate (Chart VII) became markedly accelerated. Six hours after the intradermal injection, a local urticaria appeared round its site and was accompanied by a sharp but transient delay of coagulation rate, the whole change lasting only two hours. During the following seven days of observation the coagulation rate remained accelerated.

Comparing these observations with those made in the foregoing cases of haemophilia, and setting aside the changes caused by the urticarial reaction as an intercurrent event, it appears that the results obtained in the normal are similar, though naturally much less marked, to those obtained in the cases recorded. It may, therefore, be stated that the intradermal injection of the antigenic protein within the anaphylactic period is capable of causing an increase in the blood-coagulation rate of the individual.

I desire to tender my most sincere thanks to Sir Archibald Garrod, K.C.M.G., for his kind permission to publish the notes of the two cases recorded.

Discussion.

It is not intended to enter into an intimate discussion of the theories of the causation of haemophilia, for a full bibliography of the subject may be found in the monograph by Bulloch and Fildes (3): neither is it necessary to describe in detail the modern theories of the coagulation of the blood. The present view of the causation of haemophilia appears to be, in general terms, a congenital deficiency in that part of the organic coagulating complex, which is responsible for the production of thrombin, by whose agency fibrinogen becomes converted into fibrin. Sahli (4) first suggested that haemophilia might be due to a deficiency of thrombokinase, and in later years Morawitz and Lossen (5), working with haemophilic blood obtained by vein-puncture, claim to have substantiated this view. Addis (6) concludes that there is not only a deficiency of the thromboplastic substances, but that in haemophilic blood they are required in larger quantity than in normal blood to effect clotting. It therefore appears that haemophilia may be classed as one of the ferment-deficiency diseases with a strong hereditary association, similar to other ferment-deficiency diseases such as cystinuria, alcaptonuria, &c. However, the deficiency of the thromboplastic substances is not absolute but relative, for from the results obtained in the present cases it is seen that if the necessary stimulus can be provided, the coagulating complex becomes apparently normal in action. In any case it seems to have been proved that the delayed coagulation is due to a deficiency on the organic side of the clotting mechanism, and not on the inorganic side, e.g. to a lack of calcium salts, though a case has been recorded by Hess (7) where absolute calcium deficiency was present in addition and doubtless acted as an adjuvant factor.

Since this organic deficiency has been recognized as the underlying cause of the condition, its treatment has been centred on attempts to supply the missing substances, and this has hitherto been effected by the passive means of serum injection or blood transfusion, and there is much variation as to the reported

efficacy of these measures. Laroche (8) found that in 'sporadic' haemophilia' normal coagulation time was obtained in two days following an injection of normal horse serum: further, that the effect persisted for over twenty days, and the blood returned to its former condition in two or three months. In family haemophilia he found that coagulation was accelerated, but remained abnormal. On the other hand, Baum (9) treated three cases of haemophilia by serum injections: in two the injection proved valueless, and in the third case some slight effect was produced. Schwarz and Ottenberg (10), after concluding that haemorrhagic disease of the newly born is due to a thrombokinase deficiency, found that in their cases 20 c.c. of normal horse serum produced no effect on the coagulation rate. Schiffers (11) reports a case in which a large haematoma formed at the site of injection with continued bleeding from the needle puncture, though this was the site of highest serum concentration. Fiessinger and Montaz (12), studying a case of a war wound in a haemophilic, found no change occurring in the coagulation time after horse or ox serum injections.

In the present cases, the primary injection of serum may perhaps have caused a slight temporary decrease in the coagulation rate, which cannot be said to have lasted for more than two days. It must further be remembered that the patients were, in one case, still bleeding, and in the other a severe haemorrhage had only just been controlled, at the time of injection. Wright (13), quoting Sahli, states that the latter points out that during, and for a period following, haemophilic haemorrhages coagulation times as short or even shorter than those of normal blood may be obtained. On the whole it would therefore appear that the results of simple serum injections are not satisfactory, and the danger of anaphylactic shock would in certain circumstances preclude their repetition.

Blood transfusion is of the greatest use as an emergency treatment of grave haemophilic haemorrhages. Bernheim (14) finds that a very small amount of transfused blood will bring about an almost immediate cessation of the haemorrhage. Unger (15) records seven cases of haemophilia treated by transfusion with good result, but states definitely that transfusion cannot be regarded as a cure of the condition, though it is a specific remedy for the actual haemorrhage. The following case recorded by Hahn (16) substantiates this view:

Date.	Coagulation time.	
Mar. 22, 1910	15 minutes	
Mar. 25, 1910	15 minutes.	Before transfusion
	7 minutes.	After transfusion
Mar. 28, 1910	18 minutes	
April 6, 1910	12 minutes	

and a similar picture is obtained in the first case recorded in the preceding paragraphs:

Transfusion.	Serum.	Haemorrhage.	Joint Effusion.
9.3.18			
		1.5.18	3.5.18
	5.5.18		
8.5.18			
18.5.18			
7.6.18			7.6.18
		17.6.18	
19.6.18			
		21.8.18	
			18.9.18
			15.1.19
	17.1.19	17.1.19	
	14.3.19	14.3.19	14.3.19
		26.3.19	

It must be concluded therefore on the evidence given, that the prolonged fall in the coagulation rate of the two cases recorded is in some way due to the presence of the anaphylactic state, and that this method of inducing increased coagulability of the blood is essentially active.

In order to attempt, on this assumption, to correlate the present findings with our knowledge of anaphylactic phenomena, it will be necessary to examine the facts that have been recorded in connexion with this condition. It must, however, be realized that the views quoted have been formed on experimental results in animals, and that our knowledge of anaphylactic phenomena in the human being is relatively small.

The anaphylactic state is induced by the introduction of a foreign protein directly or indirectly into the circulation. After an incubation period of eight or ten days, the subject is said to be anaphylactic or sensitized to the particular protein used at the primary injection, and a second injection of the same material given subcutaneously or intravenously will cause a syndrome of symptoms of considerable severity, culminating perhaps in death. If, however, the second or intoxicating dose is minute in quantity and is injected into the skin layers, gross general symptoms do not occur, but at the site of injection a reaction is obtained, as has already been described.

Of the anaphylactic state in man little is known, but a few points in relation to it may be mentioned. In all three experiments in the present two cases, and also in the control, sensitization was shown to be present by the twelfth day after the primary injection, on the evidence of the intradermal reaction. P. E. Weil (17), in treating haemophilia by repeated serum injections, makes no mention of anaphylactic phenomena, though in two cases which may be quoted their appearance might have been expected.

	Date.	Injection.
A.	March 16, 1907	10 c.c. antidiphtheria serum subcutaneously
	March 25 ,,	10 c.c. ,, ,, ,,
	June 22 ,,	20 c.c. ,, ,, ,,
	Oct. 13 ,,	20 c.c. ,, ,, ,,
	April 3, 1908	20 c.c. ,, ,, ,,
B.	July 6, 1906	20 c.c. ,, ,, intravenous
	July 13 ,,	20 c.c. ,, ,, ?

The duration of the sensitized state in man is also uncertain. The first case (Chart I) shows an anaphylactic period lasting certainly for twenty-nine days, and possibly thirty-two. The patient had also been given horse serum in January, 1919, but at the massive subcutaneous injection on admission two months later, no anaphylactic symptoms appeared, showing that the period of sensitization had passed off. If in haemophilics the reduced coagulation time can be regarded as a sign of the presence of the anaphylactic state, this condition has lasted in the second case (Chart V) for a period of forty days. In the first of Weil's cases quoted above, anaphylactic phenomena might have been expected on March 25 at the second injection, even though it was only the ninth day from the primary dose: failing that, symptoms might have occurred on June 22. As, however, no mention of such symptoms is made, it must be presumed that the period of sensitization commenced after March 25 and passed off before June 22. It is also possible that the injection of March 25 put the patient into a refractory phase, even though the incubation period was so far advanced.

The fundamental reasons and causes of anaphylactic phenomena have been the subject of much discussion, and Zinsser (18), after a review of the various theories on the nature of this reaction, regards it in conclusion as an acute intoxication caused by a poison produced by the proteolytic action of complement on the antigen-antibody complex. As regards the site of the reaction, there appears to be two schools of thought. Friedberger (19) and Friedemann (20), studying the symptoms caused by a toxin which was obtained by the action of complement on the antigen-antibody complex *in vitro*, and which gave on injection symptoms similar to those of anaphylactic shock, place the site of reaction rather in the blood stream, excluding a primary reaction on the part of the fixed cells. In terms of Ehrlich's side-chain theory it is in their opinion the circulating rather than the sessile receptors which play the greater part. Pearce and Eisenbrey (21) on the other hand, found results which indicate a participation of the fixed cells. Weil (22) in a series of papers concludes that the circulating antibody plays a small and unimportant part in anaphylactic shock, whereas the cellular or fixed antibody is responsible for the train of symptoms which occurs. Gay and Southard (23) disbelieve the idea of toxin formation in the blood stream, regarding the whole condition to be of a localized physical nature, affecting the nerve cells of the respiratory centre, rather than a generalized chemical reaction. Zinsser (18) correlates these apparently opposed views by suggesting that probably intravascular and intracellular union with antigen occurs, the circulating and sessile receptors both taking part, but whereas in the lesser anaphylactic reactions the sessile receptors are predominant in effect, in cases of sudden death from anaphylactic shock it is the circulating receptors which play the greater part.

Our knowledge of the action of antibodies both in anaphylactic conditions and in bacterial infections would lead us to suppose that they resemble proteolytic ferments to some extent, and when the exciting agent is a non-proto-

plasmic colloid solution, such as a serum or a single proteid, it would be expected that the antibodies produced by the somatic reaction would be more proteolytic in quality than in the case of a bacterial infection where living protoplasm is present, and the invaded organism requires other and more complex means of withstanding the attack. Pfeiffer (24) demonstrated an increased peptolytic power in the serum during anaphylactic shock, and in a more recent investigation Jobling, Petersen, and Eggstein (25) obtained a series of interesting observations in relation to the protease content of the serum. They found that the injection of the sensitizing dose had practically no effect on the serum-protease content, but that as the incubation period proceeded it became progressively increased. Acute anaphylactic shock was accompanied by an immediate and considerable increase in the serum-protease, and they conclude that the phenomena of shock are brought about by the proteolytic action of a non-specific protease and involve not only the serum but also the cells of the organism, the latter probably primarily. They also note a fall in the antiferment titre and suggest that the specificity of the reaction depends not on the protease, but on the rapid production of the ferment and the changes in the serum which cause the fall in antiferment titre. This view is somewhat similar to Zinsser's suggestion that a double reaction occurs, partly intravascular and partly intracellular.

If such a double reaction occurs, it would be presumed that it is either local or general, or localized primarily with a secondary generalization. The evidence of investigators tends by its diversity to indicate a reaction of a general nature, affecting the somatic cells as a whole. Gay and Southard (23), as already stated, localized the reaction to the nerve cells of the respiratory centre: Pearce and Eisenbrey (26) favour the nerve endings: Manwaring (27), by a series of experiments in which various organs were short-circuited from the general circulation, regards the liver as in some way directly responsible. Weil (28) concludes that all the symptoms of anaphylactic shock may be referred to the direct action of antigen upon the cells of the sensitized liver, though the blood plays an essential part in the reaction. In this connexion it may be of interest to note that Coca (29), investigating the cause of death following blood transfusion from heterogeneous species, suggests that besides the action of specific agglutinins there may be an additional element concerned in the aggregation of corpuscles which cause occlusion of the pulmonary circulation, and that this factor may arise from the vascular endothelium of the capillary wall. In view of these findings, and of the evidence quoted in the last paragraph, the occurrence of a general rather than a local reaction in anaphylactic shock is suggested.

In cases of acute shock in animals, certain changes have been constantly observed in the coagulation time. It is generally agreed that the blood becomes rapidly incoagulable, and this phenomenon has been explained on various hypotheses. A few observers, however, have also found a period of increased coagulation time. Lee and Vincent (30) noted that in moderate cases of shock

which recovered, the coagulation time was but little altered. Bulger (31), when experimenting with rabbits, found that in four animals the first specimen of blood examined after shock had been induced showed a decreased coagulation time. He concludes that the delay in coagulation rate usually found is due to an interference with thrombin production, and it has already been mentioned that the condition of haemophilia is now held to be due to a deficiency at the same stage. The finding of a decreased coagulation rate in the earliest stages of shock suggests the probability of a double reaction in this process, namely, an increase of thromboplastic substances followed by a relative or absolute decrease. In the condition of peptone poisoning, which is in many ways analogous to anaphylactic shock, a very similar phenomenon has been observed. Peptone and protein split products when introduced into the circulation cause the blood to become incoagulable, and a train of symptoms resembling those of anaphylactic shock may follow. Vaughan (33) found that if proteoses were injected in massive doses death might occur from intravascular clotting owing to the rapid decrease of the coagulation time; if, however, the animal lived there followed an increase or even a complete loss of coagulability of the blood. Nolf and Herry (1) found that small doses of peptone, introduced slowly or by absorption from the subcutaneous tissues, caused a decrease in coagulation rate, and on these grounds introduced the injection of peptone solutions as a therapeutic measure in the treatment of haemophilia. They suggest in explanation of this phenomenon that the peptone acts on the leucocytes, causing them to secrete thromboplastic substances, and this action extends to the cells of the vascular endothelium, whereas incoagulability is due to a reaction to the foreign substance on the part of the liver, the rapidity of the hepatic reaction depending directly on the rapidity of the injection of antigen. In the modern method of treatment of certain conditions by 'protein shock' (34) a similar period of decreased coagulation time followed by a prolonged time has been noted. Widal (35), recording a case of 'alimentary anaphylaxis' with urticaria, found a period of hypercoagulability of the blood following ingestion of the intoxicating protein. Shattuck (36), however, finds only delayed coagulation both in cases of urticaria and of serum sickness.

With these facts before us, it may now be possible to correlate the findings in the present cases with the recorded observations of anaphylactic shock in animals. There can be little doubt that the fall in coagulation rate occurring in these cases is directly due to the production of the intradermal reaction, for it has been shown to occur within two hours of the injection, and on two occasions when no haemorrhage had occurred for several days previously. It is therefore misleading to term the intradermal reaction a localized occurrence in the true sense of the word, for it is difficult to believe that so small a disturbance, local in appearance, can influence the tissues and circulating blood so profoundly if it is purely local in effect. It has been indicated that the changes in blood coagulation may possibly occur in two stages in anaphylactic shock, the first of which is an increased and the second a decreased coagulability, and it would seem

probable that by the use of the intradermal method, the phenomena of general anaphylactic shock are so modified and attenuated that only the first stage is obtained. If this is the case the importance of very mitigated shock as obtained by the intradermal method is obvious: for if a more severe generalized reaction were obtained, it would be expected that the coagulation time would either remain unchanged or that it would increase. This may be the explanation of Lee and Vincent's findings of an unchanged coagulation rate in animals where shock was mild and recovery followed. It may be supposed that by the intradermal injection of a protein to which a haemophilic patient has been sensitized minute quantities of a substance, perhaps a product of proteolysis, become liberated in the body fluids, insufficient in amount to cause gross signs of anaphylactic shock, but sufficient to stimulate the production of thromboplastic substances.

But it is improbable that the reaction is so relatively simple in nature. For did the fall in coagulation time depend on the presence of a non-specific split protein, one would expect that in the preanaphylactic period during the absorption of the large sensitizing dose, a fall in coagulation time would occur: for presumably during this period the foreign protein is being dealt with by the body ferments and proteolysis is occurring. But no such acceleration occurs, and two hypotheses may therefore be suggested: either that the cleavage products of the same protein by the ordinary somatic ferments and by the medium of the antibody alexin complex differ in nature, or that the split protein products are the same, but that the cells have undergone a change in regard to their reaction to such break-down products. Of the two it is more probable that a modification of the second theory affords the true explanation.

The duration of the effect of the intradermal injection presents a further difficulty in explanation. Weil (37) was able by the use of precipitation methods to detect the presence of horse serum in the circulating blood of a man for three weeks after the intrathecal injection of 100 c.c. Denzer (38), experimenting with guinea-pigs, showed that antigen and antibody could be demonstrated as coexisting in the cells and blood of the animals for a period of seventeen days following injection. On these findings the process of acute shock could be understood, since it is an immediate reaction, but the prolonged effect of the modified reaction still remains obscure. In considering the proteolytic theory of anaphylactic shock, Weil (39) writes as follows:

'A very common theory maintains that the antigen undergoes a sort of digestion, a process in which the complement acts as a proteolytic ferment, and the antibody, also known as amboceptor, serves as a bond to unite these two substances. In support of this theory, we have the observed fact that mixtures of antigen and antiserum when incubated present definite chemical evidence of protein decomposition. Recent studies, however, have shown that it is not the antigen but the antiserum itself which undergoes this change. . . .'

He goes on to mention that the diphtheria toxin-antitoxin complex may be dissociated with recovery of unchanged toxin, and also that the resolution of precipitate formed by the interaction of antigen and antiserum will yield

unchanged antigen. Finally, he regards the proteolytic theory of anaphylaxis as untenable.

But if, as is suggested, it is the antiserum which undergoes proteolysis, the explanation of the prolonged effect of the intradermal reaction becomes simplified. For in this case the antiserum acted on will be the circulating serum of the subject's blood, and Weil (28) has shown in another place that the blood is an essential factor in anaphylactic shock in a perfused liver, the passage of antigen in Locke's fluid causing no effect.

There exist then at the time of injection of the second or intoxicating dose, antibody and antigen in the blood and antigen and antibody in the cells, and the introduction of fresh antigen causes a reaction between these various factors with the production of shock. From the relatively minute size of the antigen dose required at the second injection, and from its marked and prolonged effect, there is a strong inclination to regard its action as that of a catalyst in a chemical reaction. It is probable from Weil's findings that the symptoms of shock are produced by the reaction of fixed antibody only, the circulating antibody playing no active part. It may even be the case that circulating antibody plays a protective part, combining with circulating antigen to produce an inert body, in a manner similar to the action of tetanus antitoxin passively introduced after the toxin has been absorbed into the system. For here the circulating toxin becomes inactivated, but that stimulation of the nerve cells which have fixed the toxin still continues is shown by the prolonged muscular spasm which is not affected by further antitoxin injection. The circulating antibody in anaphylactic shock may therefore be disregarded, and the whole interest centred on the fixed antibody. Though these factors, antigen, antibody, and alexin are all present in the system by the end of the incubation period, yet signs of shock do not occur unless fresh antigen is introduced at the intoxicating injection: this is perhaps a further reason for regarding its action as catalytic. In the presence of this catalyst, the following reaction may occur. Intracellular proteolysis of the fixed antigen-antibody complex is set in motion, but this proteolysis may occur not at the expense of antigen but of the elements produced by the subject, either alexin or antibody, of the fixed cells: since the presence of blood is essential for the reaction to occur, it is probable that both antibody and complement are affected. In this way proteolysis of the antiserum occurs, and this would explain the results quoted by Weil. Further, Dale and Walpole (40) found that a powerful thromboplastic activity was produced in serum which had been subjected to a slight degree of tryptic digestion, and this would account for the thrombogenetic activity which follows the intradermal reaction and which causes the marked fall in coagulation rate in the present cases. If this proteolytic process occurs, it would be supposed that on the destruction of alexin and fixed antibody the attached antigen molecule would be cast off from the cell and become free; but the cell has in the process undergone a partial or complete desensitization. If partial, it will now require, following Weil's work, a larger amount of antigen to cause it to react than

previously: if complete desensitization has taken place, no reaction will occur at all. In this way, by the casting off of antigen units by the cells the antigen content of the blood is maintained, and the anaphylactic state continues; but since the partially desensitized cells require continuously an increasing amount of antigen to unite with them to produce a standard reaction, the anaphylactic state passes gradually away. The point when the patient fails to react to a further antigen injection will therefore occur either when the free antigen has been eliminated from the system or when the antigen concentration is too low to cause any reaction on the part of the partially desensitized cells. One might, therefore, conclude that in complete anaphylactic shock rapid proteolysis of the nature described occurs, with a subsequent poisoning of the reacting cells: if the animal recovers, desensitization would be expected to have occurred, and this is in harmony with experimental findings. Further, in the modified form of shock produced by intradermal injection of the intoxicating dose, it is possible that gradual desensitization occurs, resulting in a consequently prolonged period of proteolytic action, thus accounting for the duration of the period of increased coagulability of the blood.

The relation of the return of the haemophilic state and the cessation of anaphylaxis requires a few words of comment. It will be noticed (Chart I) that the return of haemophilia, as signified clinically by a small joint effusion and *in vitro* by a rapid rise of coagulation rate, occurred at a time slightly previous to the cessation of the anaphylactic state, but while the patient was still sufficiently sensitized to give a slight reaction to an intradermal injection. This would suggest that there is a minimum concentration of the products of anaphylactic proteolysis by which the coagulation rate is controlled, and that as the anaphylactic state passes off, this concentration falls below the minimum, with a consequent return of haemophilic symptoms. From this it might be expected that the control of blood coagulation would fail earlier or later before the cessation of the anaphylactic state, in proportion as the subject presented primarily a greater or less degree of deviation from the normal in respect of the coagulation rate of his blood. There is some evidence in support of this theory, in that Case I remained with normal coagulation for a period of twenty-nine days after the intoxicating dose when sensitized to horse serum, whereas, up to the time of writing, Case II, sensitized to the same protein, has remained normal for a period of over forty days. In the matter of coagulation times, Case I showed a greater degree of variation from the normal than Case II.

Conclusions.

1. The intradermal reaction is a modified form of anaphylactic 'shock', of general as well as of local significance, and in which the stimulation of the thrombogenetic functions of the somatic cells is a salient feature.

2. The changes in coagulability of the blood in anaphylactic shock occur in two stages: a period of acceleration which occurs early, followed by a period of

retardation ; further that the predominance of the former or the latter depends on the lesser or greater severity of the shock.

3. The intoxicating injection in a sensitized individual may act as a catalytic agent in inducing the intracellular reactions which constitute the anaphylactic phenomena.

4. In cases of haemophilia the duration of the effect of the intradermal reaction is dependent on the duration of the anaphylactic period. But the shorter or longer duration of this effect is also directly dependent on the greater or lesser severity of the haemophilic condition.

Addendum.

The following case may be of interest, as from the therapeutic point of view it must undoubtedly be regarded as a failure to control the haemophilic condition. It presents, however, certain points of interest.

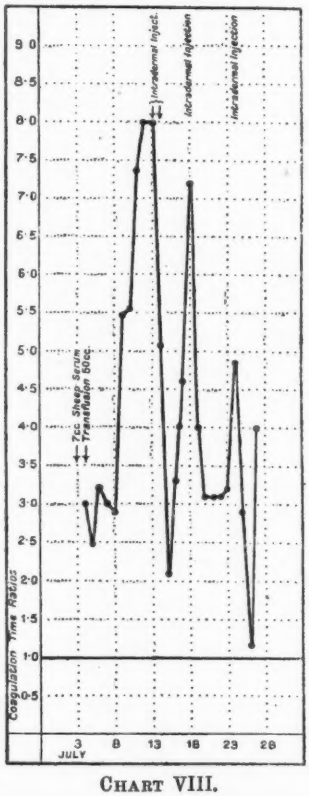


CHART VIII.

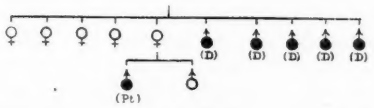
Case III. C. T., aged 4 years. (Chart VIII.) The patient was brought to hospital for uncontrolled epistaxis, which had continued for some days: on

admission he was very blanched, but had no respiratory distress. The history of the case is as follows:

At 9 months.	Prolonged bleeding following circumcision.
„ 12 „	Tendency to bruise noticed.
„ 13 „	Fell out of the perambulator and knocked out a tooth. Profuse bleeding from the gums for five days: admitted to hospital and found to have a large effusion of blood over the right buttock extending to the scrotum: ecchymoses on the legs; melaena; haematuria, epistaxis.
At 16 months.	Severe bleeding from a small cut on lip: 5 c.c. horse serum given.
„ 23 „	Epistaxis: scattered ecchymoses on the legs.
„ 24 „	Epistaxis: 5 c.c. horse serum.

The frequent occurrence of epistaxis is noticeable, and also the absence of a history of joint troubles.

Family history.



♂ = Haemophilic. D. = Died. Pt. = Patient.

All the patient's uncles died from haemorrhage; the history of the male members of the grandmother's family could not be obtained.

On admission 7 c.c. of normal sheep serum were injected subcutaneously, but the epistaxis was not stopped. Transfusion was therefore performed by the indirect method, 50 c.c. of the father's blood being given. The haemorrhage stopped immediately. The transfusion was followed by a temporary acceleration of coagulation rate. On the sixth day after admission the coagulation time became greatly prolonged and the delay increased until it was very marked. No bleeding, however, occurred externally, though a small subcutaneous haemorrhage appeared in the lumbar region. On the tenth day from admission, when the coagulation rate had become apparently stationary with a very marked degree of delay, an intradermal injection of 0·2 c.c. sheep serum was given. The reaction following it was not very well marked, but on the next day the coagulation rate was found to have been considerably accelerated. As it was, however, still much delayed, a second intradermal injection was given, producing a well-marked reaction and a further acceleration. The normal base line was not reached, however, and the injection appeared to have no effect in controlling the rate at a lower level, for a second rise immediately ensued. Altogether four intradermal injections were given, and though the effect was in no case prolonged, each was followed by an immediate acceleration of the coagulation rate.

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FAT METABOLISM IN HEALTH AND DISEASE WITH SPECIAL REFERENCE TO INFANCY AND CHILDHOOD

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The present paper is the outcome of a series of observations originally made on the digestion and absorption of fats in cases of marasmus or infantile atrophy. These yielded results which encouraged a similar inquiry into cases of rickets and tetany, and it is with these three conditions that I propose to deal. The results obtained in each will be given separately, and will be followed by a discussion on the factors to be considered in determining whether the absorption of fats in these diseases is normal or not.

1. *Method of Investigation.*

The faeces in each case were collected on a metabolism bed in the usual way, and afterwards dried in a weighed porcelain basin over a steam bath. They were then finely powdered in a mortar and a sample of about 2 grammes taken for analysis. The sample was placed in a silica basin and about 15 to 20 c.c. of ether were added. The sample was then ground up in the ether, which was then filtered through a fat-free filter-paper into a fat-extraction flask of known weight. The process was repeated several times till about 100 c.c. of filtrate were obtained, after which the ether was distilled off and the residue dried and weighed. The residue contains the neutral fat and free fatty acids. This was again dissolved in neutral alcohol and then titrated with N/10 caustic soda. From this the amount of free fatty acids was determined.

The residue left from the original extraction was then treated with a few c.c. of 50 per cent. HCl and evaporated almost to dryness over a steam bath. By this means the soaps were split up and free fatty acids liberated. These were then extracted with ether as before and weighed.

In a few cases, the soluble soaps were determined by extracting a sample of faeces with hot water and filtering into a separation funnel. The soaps were then

split with a little HCl and the free fatty acids extracted with ether. The soluble soaps were small in amount and were determined in practically all cases with the insoluble soaps.

2. *The Digestion and Absorption of Fats in Infantile Atrophy.*

Infantile atrophy, marasmus, or alimentary decomposition of Finkelstein is a disease of nutrition. Holt defines it as 'the extreme form of malnutrition seen in infancy occurring, so far as is known, without constitutional or local organic disease. It is a vice of nutrition only.' The cases in which the following examinations were carried out correspond with this definition. Tuberculosis, syphilis, coeliac disease, and pyelitis were specially excluded, as was also prematurity.

Clinically, in the treatment of this condition, improvement very frequently occurs when the milk fat is reduced to a third of its usual percentage, while the carbohydrate and protein remain constant, and especially when such a fat-weak milk has added to it varying amounts of sugar to bring the calorific value of the diet up to energy requirements. In these atrophic cases there is a non-deposition of fat in the tissues, and this has led to most inquiries being directed towards the fat metabolism. Many authors have attempted to show that there is a diminished absorption of fat, and others that the condition is due to the abstraction of salts from the tissues in consequence of increased soap formation. I propose to limit my present inquiry to the question of fat absorption.

Digestion of fat in infantile atrophy. The amount of neutral fat present in the faeces is a measure of the fat splitting in the intestine, and so is an indication of the activity of the pancreatic lipase. It has been stated by some authors (1) that there is a greater or less diminution or weakening of the digestive ferments in infantile atrophy, and that this is especially true of the fat-splitting ferment. Hecht believes that there is a connexion between the severity of the disturbance and the diminution in the amount of lipase. In twenty-two examinations of healthy stools and twenty-two of atrophic made by me, the extent of fat splitting, as measured by the neutral fat recovered in the faeces, is shown in Table I.

TABLE I. *Showing the Percentage of Fat split in the Faecal Fat.*

	Maximum.	Minimum.	Average.
Healthy	100·0	87·9	95·2
Atrophic	100·0	71·4	91·9

There appears, therefore, to be practically no diminution or weakening of the pancreatic lipase, and it must be concluded that in infantile atrophy the digestion of fats is carried out as well as in normal infants. These figures correspond closely with the results of Keller and Hecht, who found good fat splitting even in children ill for a long time. Keller, in six investigations, found 95 per cent. of the fat split. According to Freund, however, under certain pathological condi-

tions (not stated), there is a lowering of fat splitting when fat absorption is interfered with, and, conversely, that low fat splitting leads to low absorption.

Absorption of Fat in Infantile Atrophy. The figures given by various observers for the percentage absorption of fat in atrophy and other conditions show considerable variations. Freund (2) gives an absorption of 90 per cent. and 97 per cent. of fat in two atrophic cases, and in a third 81·8 per cent. The same author states (3) that, even in chronic pathological conditions, there is little loss of fat in the faeces, and again (4), that the few estimations of fat absorption which have been made in sick infants allow us to conclude that at times a considerable portion of the fat escapes absorption, but metabolic investigations have not yet determined losses of fat of a sufficiently marked degree to jeopardize nutrition. He also states that the so-called soapy stools show no impairment of fat absorption, and he gives tables showing a percentage absorption of over 90 per cent. in cases where the percentage of insoluble soaps in the faecal fat was high (5).

Bahrdt (6) gives results in cases passing soapy stools, and here the percentage absorptions are given as 82·4, 83·2, 81·9, and 86·0 compared with 93 per cent. for a breast-fed baby passing a normal stool. L. F. Meyer (7) examined an atrophic infant, receiving half milk, and found, during five periods, the percentage absorptions of fat to be 74·2, 24·9, 51·0, 68·3, and 78·6. Fife and Veeder (8) in two cases of atrophy found that the fat absorption was less than in healthy children. Bosworth et alii (9) state that, by decalcifying cow's milk, there is an increased absorption of fat. An analysis of their cases is given in Table II. It will be seen that their results do not agree with those of Holt, Courtney, and Fales (10), who suggest that the bulk of the faeces in Bosworth's cases had something to do with the low absorption. It will also be noticed that my own results differ from both, and an explanation of these differences will be given later.

TABLE II. *Analysis of Percentage Absorptions of Fats.*

Percentage Absorption of Fat.	Percentage of Cases in which different Absorptions obtained.		
	Bosworth.	Holt.	Author.
Over 95 %	0·0	31·3	18·1
Over 90 %	8·7	56·3	43·1
Over 84 %	43·5	90·6	52·1
Under 80 %	47·8	6·2	45·9

Talbot and Morse (11) remark that there is little doubt that increased peristalsis results in an increased loss of fat in the stools and that increased loss of fat may occur in any diarrhoea. Usuki (12) found that the addition of large amounts of malt extract to the food of an infant with alkaline stools caused the fat loss to increase from 10 to 15 per cent. Talbot and Hill record similar results for lactose. They found that, with good digestion, the absorption of fat was 90 per cent., and that during a sugar diarrhoea it dropped to 75 per cent. We have also the statement of Cammidge (13) that in artificially fed children not only is the percentage higher but the absolute quantity of fat lost is increased by more bulky motions being passed.

Finally, we have the findings of various authors that the fat intake has a considerable influence on fat loss. Freund states that the percentage of loss is constant, and Birk that the loss is proportionate to the intake. They both deduce from this that the food fat plays by far the most important rôle in faecal fat, and that the fat derived from the intestinal secretions is negligible.

It will thus be seen that no definite conclusions with regard to fat absorption can be arrived at from the figures given above. The percentage absorptions given by various authors show great variations, and it is probable that these are due to the operation of some factor which has not been taken into account.

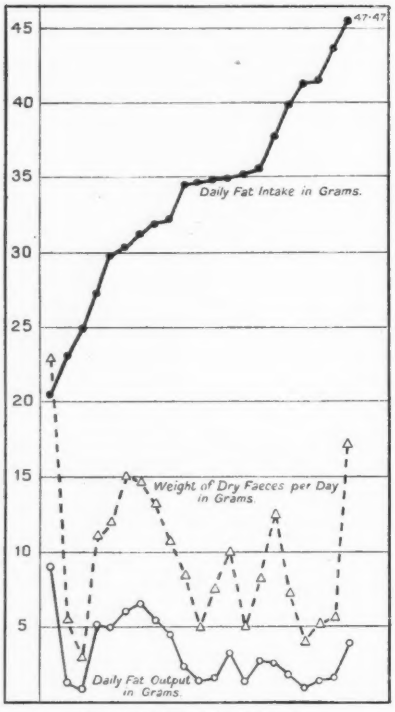

CHART I. Healthy Infants.

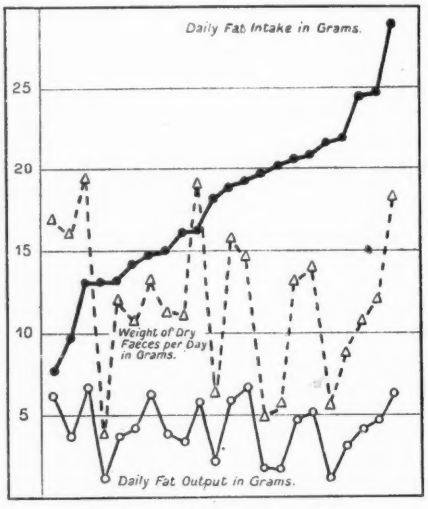

CHART II. Infantile Atrophy.

Results and discussion. In my examinations of the faeces, the sample taken was in each case approximately 2 grm., and it was noticed that the amount of fat extracted formed a fairly constant percentage of the dry faecal weight. It followed then that the total amount of fat lost in the twenty-four hours depended on the weight of the dry faeces passed and that, with a large bulky motion, the amount of fat lost was large. I therefore agree with Cammidge's statement. It must be noted that, even with a loose motion, a high absorption might be obtained, since, on evaporation of the water, the weight of dry faeces might still be small. From Charts I and II, in which are plotted out the amount of diet fat, weight of the dry faeces, and absolute amount of fat lost in the faeces, it will be seen that the fat lost varies in direct proportion with the weight of the

dry faeces, and that, while the fat intake increases, the output remains more or less constant, so that the proportion of fat lost diminishes as the intake increases. This is in agreement with van Noorden's results, which are as follows:

Fat Intake.	Amount recovered in Faeces.
grm.	%
4·2	57·1
42·2	10·9
80·2	6·36

Table III shows the relationship between the weight of the dry faeces (*a*) and the fat output (*b*). From this table, amongst healthy children, the average of the ratio *a/b* was 3·3, and in atrophics 2·9. Taking both classes together, it was 3·1, so that it may be taken that on an average the faecal fat forms approximately 1/3 of the dry faeces. This value agrees closely with that obtained for older children and adults (*vide infra*).

TABLE III. *Showing the Ratio between the Weight of the Dry Faeces and the Weight of Fat lost.*

	Healthy.			Atrophic.			
Fat Intake in grm.	Weight Dry Faeces. grm.	Weight Faecal Fat. grm.	Ratio *a/b.*	Fat Intake in grm.	Weight Dry Faeces. grm.	Weight Faecal Fat. grm.	Ratio *a/b.*
	a	*b*			*a*	*b*	
35·58	8·25	2·8	2·9	9·85	17·0	3·97	4·2
20·42	23·0	9·0	2·5	15·0	11·2	3·78	2·9
24·95	3·0	0·99	3·0	20·11	5·8	1·57	3·2
27·21	11·2	5·16	2·1	13·1	3·7	1·03	3·5
23·04	5·4	1·32	4·0	16·07	11·0	3·45	3·1
34·62	5·0	1·37	3·6	13·1	12·0	3·73	3·2
34·83	10·0	3·21	3·1	28·71	18·2	6·41	2·8
41·34	4·0	0·93	4·2	24·58	10·7	4·05	2·5
63·2	14·8	3·67	4·0	24·58	12·1	4·56	2·6
34·83	7·5	1·65	4·5	16·18	6·2	2·25	2·7
41·47	5·3	1·37	3·8	16·23	19·0	5·74	3·3
47·47	17·1	3·89	4·3	19·83	4·7	1·64	2·8
39·75	7·1	1·81	4·1	21·63	4·5	1·19	3·7
37·69	12·5	2·58	4·8	18·91	15·6	5·60	2·7
43·62	5·6	1·60	3·4	20·4	13·1	4·71	2·7
34·62	8·5	2·43	3·4	20·4	14·1	5·38	2·6
35·13	5·0	1·48	3·3	14·23	10·6	4·35	2·4
32·1	10·7	4·51	2·3	13·2	19·4	6·67	2·9
29·8	12·0	4·98	2·4	7·62	16·9	6·13	2·7
30·3	15·0	6·00	2·5	21·96	8·7	3·01	2·8
31·1	14·7	6·54	2·2	19·28	14·7	6·60	2·2
31·8	13·2	5·35	2·4	14·70	13·25	6·33	2·1
Av. 35·2	9·9	3·3	3·3	17·8	11·9	4·18	2·9

In none of the papers of other observers is the weight of the dry faeces mentioned, but the results just given would tend to bring into line the varying percentage absorptions obtained. Taking into consideration my absorption results as compared with those of Bosworth and Holt (Table II), the following gives the corresponding faecal weights:

Percentage Absorption.	Average Weight of Dry Faeces in grm.	
	Healthy.	Atrophics.
Over 95 %	5·3	—
Over 90 %	7·9	4·7
Over 84 %	8·1	5·6
Under 80 %	18·8	14·5

This result is even more apparent in the following:

Percentage Absorption.	Average Weight of Dry Faeces in grm.	
	Healthy.	Atrophics.
90 to 100	7·9	4·7
80 to 90	12·4	9·4
70 to 80	14·7	13·6
Under 70	23·0	15·8

The lower values in the case of atrophic children will be found later to be due to the much smaller intake of fat. The different values obtained in Table II are probably due to the different faecal weights yielded by the different cases under observation.

It is obvious from what has been said that the bulk of faeces passed has a very important effect on the percentage absorption of fat. In any balance experiment the percentage absorption will obviously depend on two factors, (1) the amount of fat ingested, and (2) the amount excreted, or, since the fat output depends on the faecal output, on the dry faecal weight. The percentage absorption will vary with any disturbance of the relationship between these factors. The result can be expressed in the form of a general equation. If x represents the fat intake in grammes and y the fat output, then the percentage absorption is obviously $\frac{100\,(x-y)}{x}$. If the fat output, y, remains constant, then an increase in the intake, x, will raise the percentage absorption, while if x remains constant, an increase in y will lower the percentage absorption, and the limits will be reached when x equals 0 or x equals y. In the former, the percentage absorption will be 100, and in the latter 0. It follows, then, that the percentage absorption varies directly with the fat intake and inversely with the fat output, or the weight of the dry faeces, and also that, in order to judge whether a percentage absorption is normal or not, both these factors must be taken into consideration. In several cases examined, it was found that where the intake was approximately constant, the output varied considerably, and, consequently, the percentage absorption did also. What was the cause of this variation in fat output? Three reasons may be given.

1. Increased loss of fat through pancreatic insufficiency.
2. Increased loss of fat through excessively large motions being passed.
3. Increased loss of fat through some inability of the intestinal wall to absorb the excess. This is a true defective absorption.

The first point requires no discussion, since it has been shown already that there is no defect in the splitting of fats in infantile atrophy.

Regarding the loss of fat through excessively large motions being passed,

very large motions indeed would be required if the fat lost is to be great enough to affect nutrition. The following will show that in infantile atrophy loss of fat in this way is almost negligible:

	Average Weight of Dry Faeces in grm.	Average increased Excretion of Fat in grm. per Day over Healthy Cases.
Healthy	9·9	—
Inf. Atrophy	11·9	0·88

That is, on an average, the atrophic loses only 0·88 grm. of fat per day more than the healthy child.

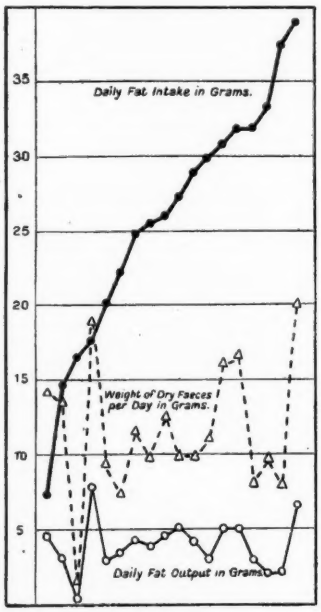

CHART III. Rickets.

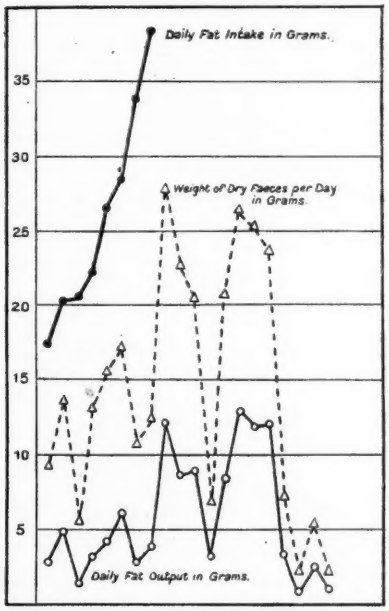

CHART IV. Tetany.

In the third case, one is dealing with a true deficient absorption. Since, on an average, the faecal fat forms 1/3 of the dry faecal weight, any fat unabsorbed will go to increase the amount normally excreted, so that the fraction 1/3 will be increased.

A reference to Charts I and II will bring out two important points. First, the fat intake has no influence on the faecal weight, and second, with an increase in fat intake, the fat output remains more or less constant, any variations in the latter depending on, and varying directly with, the faecal weight. This is important, because such variations in the fat output may affect the percentage absorption very considerably under certain circumstances. Table IV will illustrate this. Chart V represents the graph of the equation $\frac{100\,(x-y)}{x}$ for varying values of x and y on the assumption that the fat output, y,

is 1/3 of the dry faecal weight. From this it will be noticed how little the fat intake affects the percentage absorption when over 20 grm. per day. Thus, with a faecal weight of 3 grm., an increase of intake from 20 to 45 grm. per day causes the percentage absorption to increase from 95 to 97·7 per cent., a difference of only 2·7 per cent. On the other hand, with an average intake of 35 grm., an increase of the faecal weight from 3 to 12 grm. will diminish the percentage absorption from 97·2 to 88·5, a difference of 8·7 per cent. Generally speaking, it may be stated that when the fat intake is under 20 grm. per day, both fat intake and faecal weight will affect the percentage absorption though the faecal weight will be the predominant factor. When the intake is over 20 grm., the difference in intake may, for practical purposes, be neglected, and the percentage absorption will depend almost entirely on the faecal weight.

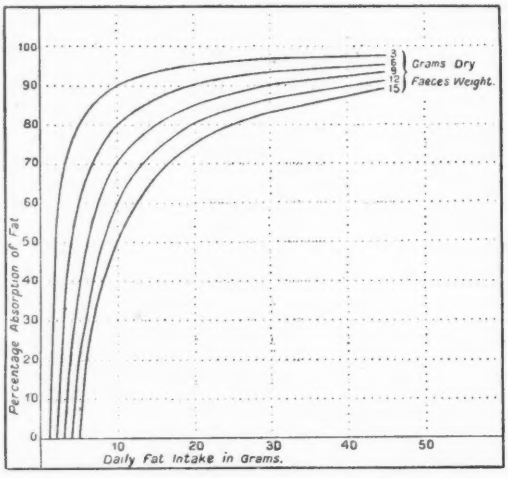

CHART V. Showing average percentage absorptions of fat with varying fat intake and varying faecal weights.

TABLE IV. *Showing the Average Percentages of Fat Absorption assuming that the Total Faecal Fat forms* 1/3 *of the Dry Faecal Weight.*

Daily Fat Intake in grm.	Total Fat in grm. excreted 1/3 Dry Faecal Weight.						
	1	2	3	4	5	6	7
5	80·0	60·0	40·0	20·0	0·0	—	—
10	90·0	80·0	70·0	60·0	50·0	40·0	30·0
15	93·3	86·6	80·0	73·3	66·6	60·0	53·3
20	95·0	90·0	85·0	80·0	75·0	70·0	65·0
25	96·0	92·0	88·0	84·0	80·0	76·0	72·0
30	96·6	93·3	90·0	86·6	83·3	80·0	76·6
35	97·2	94·2	91·4	88·5	85·7	82·8	80·0
40	97·5	95·0	92·5	90·0	87·5	85·0	82·5
45	97·8	95·5	93·3	91·1	88·8	86·6	84·8
50	98·0	96·0	94·0	92·0	90·0	88·0	86·0
55	98·2	96·3	94·5	92·7	90·9	89·0	87·2
60	98·4	96·6	95·0	93·3	91·6	90·0	88·3

It follows from what has been said that, before one can say that a percentage

absorption is normal or not, it is necessary to see whether it approximates to the average absorption calculated for a certain fat intake and faecal weight. A reference to the following Table will show how closely the observed and calculated results agree.

TABLE V. *Showing Observed and Calculated Percentage Fat Absorption in Healthy and Atrophic Children.*

	Healthy.			Atrophic.		
	Percentage Absorption Observed.	Percentage Absorption Calculated.	Percentage Fat in Dry Faeces.	Percentage Absorption Observed.	Percentage Absorption Calculated.	Percentage Fat in Dry Faeces.
	96·0	95·3	27·5	59·6	42·5	23·4
	90·7	90·5	32·1	74·8	75·2	33·8
	97·7	96·8	23·3	92·3	90·4	30·8
	94·1	92·2	24·8	92·2	90·6	27·9
	95·2	91·8	22·2	78·5	77·2	31·4
	96·6	95·8	26·0	71·5	69·4	31·1
	91·8	87·9	22·8	78·0	78·8	35·2
	95·4	94·0	24·1	83·8	85·5	38·8
	93·1	88·9	20·7	81·5	83·6	37·7
	96·3	95·7	28·7	87·7	88·5	36·0
	92·9	91·8	28·6	64·6	60·9	30·2
	95·7	95·2	29·6	91·7	92·1	34·9
	92·2	92·2	33·9	94·4	93·0	26·5
	55·9	62·4	39·1	70·4	72·5	35·9
	96·4	95·9	33·2	76·8	78·6	36·0
	81·0	86·3	46·0	73·7	76·9	38·0
	94·3	92·1	24·5	69·4	75·1	41·0
	85·9	89·0	42·2	49·4	51·0	34·4
	83·2	86·5	41·5	19·5	26·1	36·3
	80·2	83·5	40·0	86·3	86·7	34·6
	78·9	84·2	44·5	65·7	74·5	44·9
	83·1	86·1	40·6	56·9	70·0	47·8
Av.	89·4	89·7	31·6	73·5	74·5	34·8

In one or two cases, the observed absorption falls below the calculated sufficiently to say that in these cases there is a deficient absorption of fat, but in the majority the observed result coincides very closely with the calculated, and it may therefore be concluded that, in infantile atrophy, there is not any deficient absorption of fats. Taking the average of the above results, it will be seen that the average percentage absorption in infantile atrophy is only 73·5 as compared with 89·4 for healthy infants, and one would be inclined to deduce from this that the absorption was deficient in atrophy. This low value, however, is due to the low fat intake in atrophic cases in which the diet fat averaged 17·8 grm. as compared with 35·2 grm. in healthy infants.

It is apparent, therefore, that in infantile atrophy the percentage absorption of fat is not really lower than in healthy infants, and it has already been shown that in this condition the excessive loss of fat is only 0·88 grm. per day on an average, an amount which will certainly not affect the nutrition of the infant. The larger bulk of faeces in atrophy is due, probably, to a slight loss of tone in the bowel wall as a result of the poor development of the individual, and any excess loss of fat is a result and not a cause of the condition.

There is further evidence available to show that absorption of fat in infantile

atrophy is normal. In Charts I and II, in which are shown the fat intake and fat output, a steady increase in fat intake is accompanied by a more or less constant output. The difference between the intake ordinate and the output ordinate represents the amount absorbed, and it can be seen at a glance how this increases with increase in the intake.

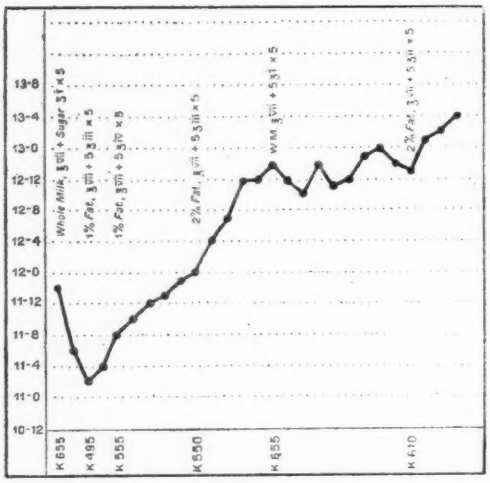

CHART VI. Weight Chart (Biweekly).

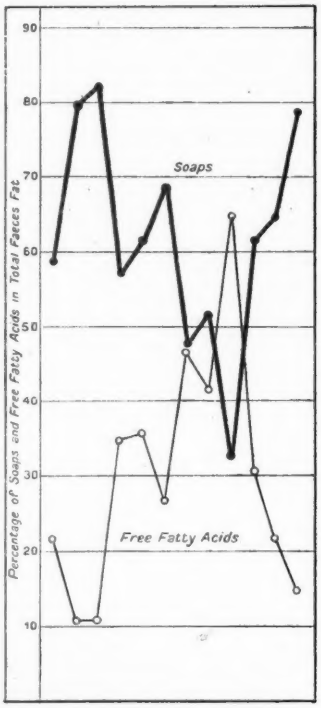

CHART VII. Showing inverse relationship between soaps and free fatty acids in the faeces.

From the clinical side there are certain facts against deficient absorption of fat being a cause of atrophy. Improvement frequently follows feeding on a fat-weak milk mixture prepared by diluting whole or pure milk with skim milk. This reduces the milk fat without affecting protein or carbohydrate. By mixing two parts of skim milk with one of whole milk, an approximate 1 per cent. fat milk is obtained and the calorific value of the diet is raised to meet requirements by adding sugar (*vide* Chart VI). Such children, when fed on whole milk, absorb in absolute figures, even with a low percentage absorption, a larger quantity of fat than when fed on a fat-weak mixture, so that evidently the condition is not due to a fat starvation.

3. *The Digestion and Absorption of Fat in Rickets and Tetany.*

Digestion of fat. As in infantile atrophy, there is no evidence of any defective digestion of fat in rickets and tetany. The following table shows the percentage of fat split in these diseases as compared with healthy children:

	Maximum.	Minimum.	Average.
Healthy	100·0	87·9	95·2
Rickets	100·0	81·6	96·3
Tetany	100·0	86·0	93·9

Absorption of fat. The same tests applied in the case of infantile atrophy can be applied in rickets and tetany to determine whether the percentage absorption of fat is normal or not. In Table VI the observed and calculated percentage

TABLE VI. *Showing the Observed and Calculated Percentage Absorptions in Rickets and Tetany.*

	Rickets.			Tetany.		
	Percentage Absorption Observed.	Percentage Absorption Calculated.	Percentage Fat in Dry Faeces.	Percentage Absorption Observed.	Percentage Absorption Calculated.	Percentage Fat in Dry Faeces.
	82·6	83·8	36·0	91·4	89·4	27·0
	84·7	93·5	46·9	89·9	91·8	31·1
	83·3	82·9	32·5	85·2	80·5	25·0
	94·1	93·0	27·8	92·7	91·2	27·5
	85·4	84·4	31·2	84·2	80·5	27·2
	82·6	84·7	37·7	75·6	77·6	36·3
	83·4	82·7	36·3	78·4	80·2	36·0
	84·2	82·6	30·3	83·1	82·4	32·0
	90·0	87·9	26·9	—	—	43·5
	90·9	94·7	35·7	—	—	37·7
	37·6	34·9	32·2	—	—	43·8
	78·7	69·1	23·2	—	—	46·5
	97·0	96·9	32·2	—	—	40·8
	56·1	64·5	41·6	—	—	49·1
	85·2	87·2	38·7	—	—	47·1
	81·1	88·0	52·9	—	—	51·0
	94·5	90·2	18·6	—	—	45·6
	89·0	88·7	42·9	—	—	36·8
	—	—	—	—	—	40·0
	—	—	—	—	—	49·2
Av.	82·2	82·7	34·6	85·0	84·2	38·0

absorptions are shown. These will be found to agree fairly closely. Unfortunately, however, in a certain number of the cases of tetany, the fat intake was not determined, and in these the fat percentage of the dry faeces was abnormally large. In some of these, large motions being passed, the fat loss was therefore very great. All the same, on the average, the fat lost in tetany was about 11 per cent. higher than in health, and allowing this may be in part accounted for by the excessive loss in some cases, it would appear that in tetany fat absorption is slightly deficient. In Charts III and IV, however, the increase in fat intake is not accompanied by any increase in output, so that if there is any deficient absorption in tetany it is not marked, and the more fat presented to the patient, the more will be absorbed.

One must therefore conclude that in rickets there is no deficient absorption of fat, but that in tetany there is a slight defect, and that this, with an average motion, is insufficient to affect nutrition.

4. *The Composition of the Faecal Fat.*

As mentioned above, there is a good digestion of fat in atrophy, rickets, and tetany, and it is quite as efficient as in healthy children. The average amount of fat unsplit in the faecal fat is about 6 per cent. Soluble soaps also form a very small percentage of the faecal fat, and here my results agree with those of Usuki, who places them at well below 10 per cent. The amount of fatty acids and soaps in the faeces varies considerably, but Chart VII shows that they have a close inverse relationship to one another, thus confirming the results of Keller and Meyer. This also holds good for healthy children. It was thought from this that soap formation, i.e. insoluble soaps, occurred after absorption of the fatty acids was complete, since otherwise one would expect the free fatty acids to be absorbed and so upset the inverse relationship. To settle this point, an analysis of the faecal fat was made in a case of carcinoma with an intestinal fistula, said by the surgeon to be very high up in the jejunum. The patient was receiving a dietary of strained soup, fish, eggs, milk, bread and butter, and the following result was obtained:

	Percentage of Dry Faeces.	Percentage of Total Fat.
Neutral fat	0·45	2·43
Free fatty acids	5·65	30·58
Soluble soaps	5·80	31·40
Insoluble soaps	6·57	35·59

This shows that the insoluble soaps are just as abundant high up in the jejunum as in the faeces, but the striking thing is that complete fat splitting should occur within about 2 feet of the duodenum. The site of formation of soaps and the presence of a definite amount of free fatty acids in the faeces would indicate that a certain amount of fat has to be left in the faeces, but this point I will return to later.

The iodine value of the fatty acids combined as insoluble soaps is low and averages 10. The iodine value of the total faecal fat was distinctly higher in healthy infants than in atrophics. This would indicate that atrophic children absorb more unsaturated fatty acids than do healthy children.

I do not propose to enter here into a discussion concerning the formation of soaps in the intestine, but, from the work of Freund (3), it seems that the main factor causing soap formation is the reaction of the intestine. Bosworth et alii (9) claim that the degree of solubility of the food calcium is the factor which influences the formation of soaps, and that a high calcium intake causes a serious loss of fats as soaps. This factor may also come into play by being the source of calcium, provided the reaction of the intestine is suitable.

However, what concerns us at present is whether a soapy stool is associated

with a deficient absorption of fat. A soapy stool varies in colour from light yellow to grey. In some cases it is large and hard, and in others dry and crumbly. In my own cases, the stools were as a rule of putty-like consistency, but frequently, when a large motion was passed, they were semi-solid. Naked-eye appearances, however, are apt to be deceptive, and it would be better to limit the term 'soapy stool' to one containing a high percentage of insoluble soaps irrespective of naked-eye appearances.

I have not been able to confirm Bosworth's statement. It is immaterial whether a large percentage of soap is present or not in the faeces, because the soaps and free fatty acids vary in inverse proportion and, if the soaps are high, the free fatty acids are low and vice versa, so that the total fat in either case forms approximately the same fraction of the dry faeces and the observed percentage absorption of fat in either case is just as near the calculated result. This may be seen in the following table:

TABLE VII. *Showing the Percentage Absorptions obtained where the Soap Percentage was high and low, and that the Soaps present have little or no effect on the Fat excreted.*

Percentage of Soaps in Total Fat of Faeces.	Percentage Absorption Observed.	Percentage Absorption Calculated.	Amount of Fat Excreted per Day in grm.
86·1	96·0	95·3	1·37
88·0	90·7	90·5	3·21
84·2	97·7	96·8	0·93
86·8	94·1	92·2	3·67
87·5	95·2	91·8	1·65
Av. 86·5	94·7	93·3	2·16
42·1	92·2	92·2	2·80
39·5	96·4	95·9	0·99
32·6	94·4	93·0	1·19
51·3	91 7	92·1	1·64
27·8	94·1	93·0	2·20
Av. 38·6	93·7	93·2	1·76

It has already been shown that there is evidence to prove that the absorption of fats in infantile atrophy is normal or practically so, and yet in healthy infants the average percentage of soaps in the total faecal fat was 77·9, while in atrophics it was 60·1. The absorption of fat, where a high percentage of soaps is present, follows the same rules as stated above, and the percentage absorption will depend on the fat intake and faecal weight. In the above table the absolute excretion of fat is seen to be practically the same whether a large amount of soap is present or not, and one is therefore forced to conclude that saponification of fats in the stools in no way affects absorption. It has been my clinical experience to find soapy stools to be the rule when improvement sets in.

5. *Has Faecal Fat a Function to perform?*

Is faecal fat a pure excretion? Does it represent merely the portion of food fat unabsorbed, or is it left over in order to perform some function or other?

It is certainly worthy of note that not only in healthy infants, and in infants and children suffering from atrophy, rickets, and tetany, does the faecal fat form an approximate constant of the dry faecal weight, but the same result is obtained in older children and in adults. In two children, aged about 8 years, and convalescing from pneumonia, the fat percentages of the dry faeces were 27·7, 27·7, 33·5, and 28·5, and in three adults, 32·2, 32·2, 21·2, 33·3, 25·6, and 31·2. In the former cases, the diet was composed of milk, and in the latter, during one period, the fat of the diet was supplied as fat, and during a second period as fatty acid. Observations were made on a dog on different diets, with the following result:

Diet.	Average % Fat in Dry Faeces.
Milk and porridge	21·8
½ porridge, ½ meat	17·7
Whole meat	16·1
½ porridge, ½ meat	16·9
Milk and porridge	19·0
Lemco, casein, rice (fat-free)	14·0

These results may be compared with those of J. C. Drummond (14) in the case of rats, viz.:

Periods of 1 Week.	Average % Fat in Dry Faeces.
1	6·1
2	6·1
3	13·3
4	5·9
5	5·8

With the exception of the third period, we have again a very constant percentage of fat in the faeces of rats. It is thus clear that the fat excreted forms a fairly constant percentage of the dry faeces, and that this percentage varies in different species.

It naturally occurs to one that the fat in the faeces may act as a lubricant to the intestinal wall, or that it possibly prevents excessive absorption of water which would lead to constipation. Certainly, in loose motions, there is a tendency for the fat percentage in the faeces to rise, but on the other hand, in constipated motions, there is no tendency for the fat percentage to fall, and in one case of tetany examined, where constipation was marked, the fat percentage in the faeces was well above the average. However, from the evidence at hand, it would not be profitable to speculate further on the nature of the function of faecal fat. It is sufficient to say that the constancy of the faecal fat would suggest some special function. In one case, an adult, examinations of the faeces were made on a diet containing Lemco, casein, and rice, i.e. a fat-free diet, and the

percentage of fat in the faeces was 23·2. This approximates to the figures obtained for healthy subjects on diets containing fat. This fat might be derived from fatty changes in the intestinal contents by bacterial action or from the intestinal secretions, but this explanation does not give any reason for the constancy of the faecal fat.

6. *Summary and Conclusions.*

1. The digestion of fats in infantile atrophy, rickets, and tetany is carried out as efficiently as in healthy children.

2. The fat output in the faeces varies directly with the faecal weight and forms approximately 1/3 of this.

3. In order to determine, in any balance experiment, whether the percentage absorption is normal or not, it is necessary to take into consideration the faecal weight. When the fat intake is under 20 grm. per day, both fat intake and faecal weight will affect the percentage absorption though the faecal weight will be the predominant factor, and, when the intake is over 20 grm. per day, the intake may, for practical purposes, be neglected, and the percentage absorption will depend on the faecal weight. When the faecal weight is taken into consideration, the observed and calculated percentage absorptions agree closely. The lower average percentage absorption in atrophy is due to the lower average fat intake, this being only 17·8 grm. as compared with 35·2 grm. in healthy children.

4. There is a slightly greater loss of fat in infantile atrophy, due to the motions being larger than in healthy children, but the excessive loss, which amounts to 0·88 grm. per day, can be neglected so far as nutrition is concerned. There is no true deficient absorption.

5. In rickets, the excess loss of fat per day over that in healthy children averages 0·6 grm., an amount which is quite sufficient to affect nutrition.

6. In tetany, the excess loss is 2·4 grm. per day. This is due chiefly to the passage of larger motions than normal, viz. 14·4 grm. compared with 9·9 grm., and to a less extent to a true deficient absorption, since the fat in the faeces averages 38·0 per cent. This loss is insufficient to affect nutrition.

7. Other facts point to a normal fat absorption in atrophy, viz. the increased amount of fat absorbed with an increased intake, and the fact that improvement frequently follows the lowering of the fat content of the milk.

8. Saponification of fats in the intestine does not affect the absorption of fats.

9. The fairly constant percentage of fat in the faeces of man and other animals suggests that faecal fat has a function to perform, and that it is not a pure excretion. There is no evidence, however, to indicate what this function is.

In conclusion, I desire to thank Prof. Noel Paton, University of Glasgow, and Dr. Leonard Findlay, Royal Hospital for Sick Children, Glasgow, for many valuable suggestions and for their kindly criticism of my work.

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POSTSCRIPT.

Since writing the above, my attention has been drawn to a paper by Holt, Courtney, and Fales on 'Fat Metabolism in Infants and Young Children' (*Amer. Jour. Dis. Children*, 1919, xvii. 423). Their results agree closely with my own in normal children.

	Holt.	Author.
Average fat, % in dry stools	36·3	31·6
Soap, percentage of total fat	73·8	77·9
Free fatty acid, % of total fat	17·0	17·3
Percentage retention	88·6	89·3

It would be interesting if these results were considered as above with reference to the faecal weight.

THE MECHANISM OF POST-OPERATIVE MASSIVE COLLAPSE OF THE LUNGS[1]

By J. CHARLTON BRISCOE

With Plate 8

Historical.

Attention was first drawn to the syndrome 'Post-operative Massive Collapse of the Lungs' by Pasteur, in the year 1908. For over eighteen years he had been interesting himself in conditions which involved deficient activity in the various parts of the lungs, and on many occasions has drawn attention to these incidents.

In 1890 Pasteur published his first paper connected with the larger aspect of this subject, entitled 'Respiratory Paralysis after Diphtheria as a Cause of Pulmonary Complications' (1). This paper dealt with thirty-four consecutive cases of post-diphtheritic paralysis, in thirteen of which the diaphragm was affected. He accentuated the fact that they were severe cases. Quoting von Ziemssen, he drew attention to the conclusive signs of paralysis of the diaphragm, consisting in the reversal of the normal movements of the epigastrium and the hypochondrium, and diminished power of compression of the contents of the abdomen, resulting in weak force of cough, dyspnoea on exertion, &c.

He observed that outward movement—eversion—of the lower ribs, greater on the right side than on the left, was a noteworthy condition, and recognized it as an exaggeration of the normal, depending on paralysis of the intercostal and abdominal muscles. In five out of eight post-mortem examinations he found that the lungs were affected in a peculiar manner; large areas, especially in the lower lobes, were airless, sank in water, and were of a dark blue colour, thus resembling the collapse found in much smaller areas in broncho-pneumonia. To this condition the term massive collapse was applied. He did not contend that collapse invariably resulted, but rather that the loss of function in the lungs was, *caeteris paribus*, proportionate to the degree of paralysis of the diaphragm. He concluded, therefore, that 'paralysis of the diaphragm or other parts of the chest-wall tends to induce loss of function in the adjacent lung, which is, *caeteris*

[1] The Harris and Gale lecture, delivered Feb. 24, 1919.

[Q. J. M., April, 1920.]

paribus, proportionate to the degree of paralysis, and results in more or less collapse and oedema of the pulmonary tissue'.

In 1895 Pasteur published in the Clinical Society's Transactions (2) a résumé of sixty-four cases of diphtheritic paralysis, including those described in the former communication. In twenty cases cardio-pulmonary crises occurred, and in seventeen of these the diaphragm was paralysed. In all, he had collected thirty-two cases of paralysis of the diaphragm. He concluded that paralysis of the diaphragm or chest-wall, persistent for two days, leads to collapse of the lung. He agreed with the late Leonard Guthrie in dividing the cases into those in which the phrenic nerve was paralysed, and those in which the bulbar origin of the phrenic nerve was affected.

Guthrie's paper, which he quoted, dealt with the condition of 'Bulbar Crisis occurring in Diphtheria' (3), in which sudden attacks indicating cardiac and respiratory failure, with vomiting, recurred at intervals, but from which recovery was possible. Pain was absent. Besides describing these attacks Guthrie showed that the diaphragm can be paralysed and recover very quickly; one post-mortem showed collapse of the lung, congestion only being present in the remainder.

These two papers dealing with post-diphtheritic conditions in which collapse of the lower lobe was not infrequent, formed the basis of the work which Pasteur carried out for his next communication, the Bradshaw lecture in 1908 (4).

In this lecture he discussed respiratory movements in general, and recalled the condition associated with diphtheria. He quoted a series of cases in which, following operation, usually on the abdomen, 'collapse' attacks of the following nature occurred: pain of sudden or gradual onset was experienced in the lower part of the chest and retrosternal region, the pulse and respiration rate increased markedly, cyanosis was present, and the patient seemed *in extremis*. The lower lobe of the lung on the side affected was collapsed. The lung on the opposite side was over-active. The heart was displaced to the affected side. Fever was present. The duration of the severe attacks was not more than forty-eight hours, and in every case recovery eventually took place. A toneless condition of the epigastrium on the affected side is noted in some of his protocols, though no emphasis is laid on this point.

The statements in this paper are of importance. After discussing whether pleurisy is a factor, he says, 'I am disposed to attach more importance to the presence of acute disease below the diaphragm, if only for the reason that the evidence at present available shows that massive collapse is most often related to diaphragmatic failure, and that there are no reasons for supposing that inflammation of the pleura—with the possible exception of the diaphragmatic surface—ever leads to an arrest of diaphragmatic action so intense as to enable massive collapse of the bases to take place.' And again: 'It (massive collapse) is generally caused by paralysis of the muscles which are the direct distenders of the lungs—the diaphragm and the intercostals,—but I have also shown that

there are strong grounds for believing that reflex inhibition of diaphragmatic movement may lead to the same result, and that this observation may throw some light on post-operative lung complications.'

The position, then, at this time was, that Pasteur considered that 'massive collapse' attacks were due to paralysis or reflex inhibition of the diaphragm and other muscles distending the lungs, but he did not consider that pleurisy was of any importance.

He reverted to this subject in 1910, in the archives of the Middlesex Hospital and in the *Lancet* (5), and in 1911 in the Presidential Address before the Medical Society of London (6), and again in 1914, in the *British Journal of Surgery* (7). In these papers he obviously considered that there was a close connexion between the mechanism producing collapse of the lower lobes in post-diphtheritic paralysis, and that underlying the collapse attacks following operations.

After fully discussing the influence of different anaesthetics and quoting Bibergiel's monograph, he comes to the conclusion that very little importance should be attached to the means by which anaesthesia is induced.

He divides the cases of collapse of the lower lobes into those in which the lesion is demonstrably due to paralysis of some of the essential muscles of respiration—the diaphragm and intercostals—the collapse being often bilateral, and those in which collapse intervenes suddenly without premonitory signs of cardiac and respiratory failure. The latter are always unilateral.

He concludes that post-operative collapse is the result of (reflex) arrest of action of one half of the diaphragm.

Several of the cases have been quoted in more than one of his papers; it is therefore difficult to draw up a precise list, but the general conclusion may be drawn that collapse of one or both lobes occurs in the paralysis which follows diphtheria, that collapse of one or both lobes may also occur after operation and without symptoms, but that in the majority of 'post-operative massive collapse attacks', it is only the lower lobe on one side which is affected.

The surgical conditions under which the attacks occurred were generally abdominal operations, but it had been found after thyroidectomy, in portal pyaemia, in a case of pneumonia, and after injuries such as falls from a horse or bicycle, with bruising of the trunk but without fracture of the bones. In no case was it found to occur after a simple exploratory laparotomy.

In 2,000 cases of abdominal operations he found lung complications occurred in sixty-five instances, and of these sixty-five cases, massive collapse was noted in sixteen. The condition may therefore be considered uncommon, and the difficulty of investigation is further increased by the fact that since the introduction of antidiphtheritic serum, severe paralysis following diphtheria is much less frequent than prior to 1890.

Other work on this subject is scanty. Elliot and Dingley (8), in 1914, put forward the view that collapse is due to obstruction of the bronchial tubes by retained secretion, with subsequent absorption of the retained air. I criticized

this communication in a letter to the same journal, pointing out that 'Massive collapse of the lower lobes is a natural sequence of prolonged quiet breathing in the supine position in such people as do not use the abdominal muscles to fix their chests' (9), (10).

Crymble (11), in an article on gunshot wounds of the chest, quotes a number of cases of collapse of the lower lobes and produces radiograms of some of these. He comes to no conclusion as to the mechanism by which collapse is produced.

Pasteur's theory of the production of collapse of the lower lobes did not seem to satisfy the conditions. It has frequently been shown experimentally that paralysis of the diaphragm such as follows section of both phrenic nerves was followed by the death of the animal. It was contrary to the general teaching in regard to the movements of the diaphragm, to suppose that one half should be thus affected while the other was normal; further, it was obvious that in diphtheria the paralysed diaphragm was liable to recover much more quickly than the other paralysed muscles, and indeed Guthrie (3) had noticed that the movements of the diaphragm were frequently modified within relatively short periods. 'The muscle might act feebly or not at all, and for a time it might seem absolutely paralysed, and then again it acts spasmodically. With equal caprice it is found acting normally.'

Schroeder and Green (12), as the result of clinical observations and experimental work on animals and birds, conclude first that the diaphragm is not an essential muscle of respiration. Secondly, that the nerve supply is practically entirely dependent on the phrenic nerve. Thirdly, that after section of the phrenic, the intercostal nerve-supply is insufficient to carry on the action of the diaphragm. Fourthly, that the section of one phrenic nerve produces collapse of the lower lobe of the lung on the affected side; and finally, the destruction of one phrenic nerve in man is not necessarily fatal. In collecting the cases from the literature they quote one case reported by Schirlmeyer of a man who died rapidly after an injury which cut the phrenic nerve. No collapse of the lung is mentioned. In a second case reported by Beck, in which the patient died on the fifth day following operation, no mention is made of the lung condition.

Schroeder himself divided the phrenic nerve on the left side in a case of tumour in the neck with no bad effect except increased respiratory rate and some evidence of collapse at the base of both lungs. In short it may be said of this paper that it makes very little reference to the condition of the lungs induced by this operation.

Experimental.

In none of my experiments did I succeed by this method in producing any results corresponding to deflation of the lower lobes of the lung. The rabbits were anaesthetized and the nerve of one side divided in the neck. The most

marked results were observed when the animal was killed by chloroform seventy-two hours after nerve section. The results were by no means constant. It was generally found that deflation was most pronounced in the following order of distribution: First at the apex of the lower lobe, secondly at the extreme base, at the postero-internal angle of the lung, and thirdly a varying degree of deflation of the upper lobe where it abuts on the apex of the lower lobe. The deflation was not limited to the lung on the same side as the paralysed half of the diaphragm. The opposite lung was affected in the same areas and frequently

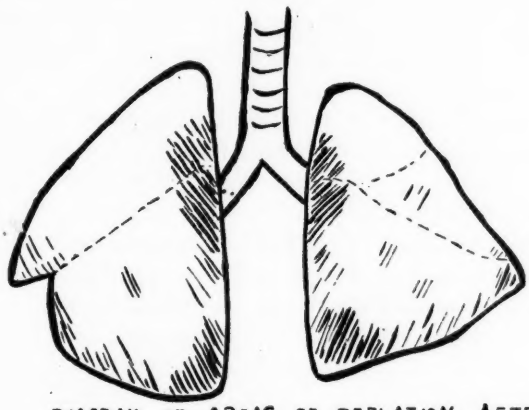


FIG. 1. Postero-lateral aspect.
The same result was obtained if the rabbit was allowed to be about, or was lying on its back under continuous anaesthesia.

to as great a degree (Fig. 1). When the left phrenic was cut, the right lung was affected as much as the left, but when the right phrenic was cut, the right lung was more affected than the left. Other portions of the lung, generally the free margins, more especially anteriorly where they are in contact with the diaphragm, were similarly affected, but in a varying degree, and sometimes not at all. The lesions seemed to cause no inconvenience to the animal; in one case a rabbit survived more than a year, and its death was in no way connected with the phrenic nerve section.

When a rabbit was examined under X-rays after section of the phrenic nerve, the paralysed half of the diaphragm could be seen to be pulled over towards the sound side during inspiration. This movement differed from the normal, when the diaphragm descended towards the caudal extremity. The main result of inspiration after phrenic section is in an axis forming an angle of about 60 degrees with the axillary part of the chest-wall. In the anaesthetized animal hooks were placed in the abdominal surface of the two domes of the diaphragm and connected with writing levers so as to record movements on the kymograph; records of the movements of the domes were then secured. If one phrenic nerve

was cut and the corresponding half of the diaphragm paralysed it was found that in the course of a few breaths the active half of the diaphragm made a greater effort and by this contraction 'picked up the slack' of the paralysed half. There was no descent of the paralysed half of the diaphragm during the inspiratory descent of the non-paralysed side, but during the expiratory ascent of the active side there was a descent of the paralysed side. This would appear to indicate that with inspiration air was drawn from the lung on the paralysed side, and, prior to expiration, while the larynx was closed, air was forced into the same lung from the healthy one. This movement was abolished when tracheotomy was performed: the lever then showed no rise or fall on the paralysed side.

Mr. Morriston Davies (13) has recently recommended section of the phrenic nerve for pulmonary tuberculosis.

The results of section of one phrenic nerve on the two lungs might be explained by the fact that there is a considerable amount of decussation in the muscles of the two crura of the diaphragm. Apart from the action of the crura, collapse on the paralysed side might be anticipated from defect of that portion of the diaphragm which arises from the lateral and anterior rib area. Functionally, however, the costal diaphragm on the non-paralysed side has lost one of its points of attachment, and therefore as a whole must produce a less effective contraction.

A second series of observations was undertaken with the object of showing whether the two halves of the diaphragm acted asynchronously, independently, or with a different excursion.

Head's (14) method with chloral and ether anaesthesia was adopted with a slight modification. The xiphisternum was separated by dissecting out the bone in the manner described by Head. The diaphragm was then underpinned by fixing it to the lower part of the sternum by a single ligature, and when this had been accomplished, the median raphe of the portion of the diaphragm attached to the xiphisternum with the cartilage was incised, and a thread attached to each half of the cartilage. By this means a record was obtained from both the right and left halves of the diaphragm, instead of a single record from an undivided slip.

Various methods were tried in the hope of influencing the contraction of one of these slips to a greater extent than its fellow. Different strengths of salt solution were injected into one or other lung by means of a catheter after tracheotomy. By adding a little carmine it could be ascertained into which part of the lung (usually the lower lobe) the injection had entered. Other liquids, such as carbolic acid, formalin, sodium fluoride, cocaine, &c., in solution, were also injected. These had no lasting effect at all comparable with the inhibition of movement of one half of the diaphragm. Injections of irritants such as carbolic acid, formalin, and tobacco sauce, were made into the pleura, also without permanent effect.

Pleurisy was induced prior to the observation by an injection of saline, to which were added dead and living organisms. During the observation paraffin wax was introduced into the internal jugular vein and allowed to pass

through the heart to produce infarction in the lung, but without any homo- or contra-lateral effect on the diaphragm.

The peritoneum was irritated by the handle of a scalpel and by the introduction of a hot wire without producing any effect upon the slips; pinching, and traction on the liver, stomach, and small and large intestine, likewise produced no response.

Electrical stimulation of the intercostal nerves was fruitless. Some differences were observed during the application of intense cold or heat to the side of the thorax, by an ether spray or by a hot poultice, the homolateral slip contracting less than its fellow, though the contraction of both slips was diminished. The greatest difference observed was produced when the animal was laid on its side without other interference. It was found that in two instances the half of the diaphragm on the underlying side contracted somewhat more freely than the upper half, while in the third case the increased action was reversed.

Observations were also made by the introduction of irritant substances, such as sand, ground glass, or carbolic acid, into the pericardium, but again no obvious change in the extent of contraction in the two halves of the diaphragm ensued.

In view of the negative results obtained from these two methods and the recognized effect of section of both phrenic nerves, the theory put forward by Pasteur that the deflation of the lower lobes was dependent upon paralysis of one or both halves of the diaphragm seemed to be untenable. No evidence of reflex arrest of one half of the diaphragm had been obtained.

The Effects of Paresis.

On reconsidering his work, two points presented themselves which could not be neglected. The first, that all his cases were extremely ill, in the one series from the severity of the diphtheritic infection, and in the other series from the fact that an extensive operation had recently been performed. Secondly, these circumstances would certainly entail the supine posture and complete rest. It seemed necessary to take this latter point into account and to consider the effect of quiet breathing in the supine posture. This investigation was accordingly made.

About this time, 1910, a patient was admitted into King's College Hospital suffering from a progressive lesion of the spinal cord at the level of the third dorsal segment. Physical examination showed that the lower lobes were solid, but contracted, and a diagnosis of massive deflation was made. The patient died, and on post-mortem examination it was found that both lobes were small and completely deflated, while the upper lobes were fully distended.

Since that period I have performed post-mortem examinations on three other cases of complete lesions of the spinal cord in the upper dorsal region, and in each instance have found a similar condition of the lungs. Deflation was not complete in a case of fractured spine dying within thirty-eight hours of the accident. In a number of soldiers in whom high paraplegia resulted from bullet

wounds the physical signs have been those of complete deflation of the lower lobes. I also saw a patient of the same type at St. Marylebone Infirmary; Dr. Whittington performed the post-mortem examination and the same condition of the lungs was present.

The lungs from the first case were retained as permanent specimens, and photographs were made from the second case and are now produced (Fig. 2, Plate 8). Unfortunately preservation allows a certain amount of diminution in the size of the over-distended upper lobes. The preserved specimens are not so realistic or reliable as a photograph, which presents a much more accurate picture. A comparison of these lungs showed that the degree of deflation of the lower lobes was similar and complete in these instances, but the degree of over-distension of the upper lobes varied considerably. Hence the conclusion might fairly be drawn that some other factor was present besides the obvious condition—that breathing was being carried out practically solely by the diaphragm. (It was obvious that in this case the supine posture would be that most generally adopted.) It also brought home the fact that complete deflation of the lower lobes occurred when the diaphragm was *the* muscle operating in inspiration.

The investigation of the condition of the lungs by the maintenance of the supine posture was made by examining patients in uncomplicated cases of abdominal operations. It was found that eleven out of thirty cases presented signs of deflation of the lower lobes. These were not selected in any particular manner, but were examined as time and opportunity allowed. Searching for any difference in the deflated and non-deflated cases, it was found that in the former class there was neither tone nor muscular action in any of the abdominal muscles, while in the non-deflated cases some muscular action was present during part of the respiratory phase. The latter had recovered sufficiently to be able to move in bed, feed themselves, talk, &c. As at first no explanation of this difference offered itself, it became necessary to institute an investigation into the action of these muscles in the normal individual in the erect and supine postures when breathing quietly and naturally. At the same time certain measurements of the chest were taken.

After having collected a large number of measurements and observations of the muscular reactions of normal individuals, the whole matter seemed incoherent, and I therefore decided to collect the extremes and investigate these somewhat more closely, and by this means was able to separate the three classes given below.

The Conditions of Normal Respiration.

During quiet breathing the amount of movement of the abdomen is roughly similar in most individuals in the erect posture, but when supine, considerable differences may be observed. In the erect posture it is difficult to say whether there is any actual contraction of the rectus abdominis muscle, and this especially

in the lower part, for the reason that the abdominal wall in these areas is tense and it cannot be stated that this is due to muscular action. The degree of tension varies, being increased at the end of inspiration and decreased at the end of expiration. The tension is chiefly increased in that part of the abdomen which lies below the umbilicus. My belief is that in these circumstances the rectus does not contract, that the underlying fascia is of itself sufficiently elastic to account for these variations in the majority of individuals, but that in a few an expiratory contraction of muscles acting on the lower abdominal wall does occur.

When, however, the examining hand is passed farther outwards into what may be termed the lateral region, situated between the planes of the anterior and posterior axillary folds projected downwards, a varying condition is found. Here the reactions are of three kinds: (A) there may be no contraction whatever, (B) there may be a contraction increasing progressively during expiration, and (C) the tone of the part may be continuous during inspiration and expiration, and there may be superadded a condition similar to that described in (B). The contracting muscle is, presumably, the ascending portion of the external oblique. The contraction is somewhat peculiar. It commences feebly, grows in strength, gives a last supreme effort, and relaxes sharply at the beginning of inspiration. This type of action occurs in all the expiratory muscles.

Posteriorly, i. e. in the regions lateral to the spine, the degree of contraction varies and is generally continuous, resulting from the fact that these muscles operate in maintaining the balance of the body. The muscles of the lateral group also assist in this, becoming tense when, by an inclination of the body laterally, that side becomes convex, and to a lesser degree on the concave side.

When the supine posture is adopted, the conditions vary to some extent. Those individuals whose lateral muscular action places them in division A, remain in that division, i. e. there is no contraction of the lateral muscles. The muscle action of those in division B may pass into division A, i. e. there is no contraction, or may remain in division B, but with diminished force of contraction during expiration. Those in division C will generally pass into division B or even occasionally into division A. This change commences immediately on the assumption of the supine posture. It may therefore be stated that in general the action of the lateral group tends to diminish. The time factor has also to be considered, and it will be found that at the end of ten minutes (which for all practical purposes is the longest time that a normal individual can be expected to remain quiescent) the strength of contraction of these muscles will have still further diminished, and, judged by the muscular action, the individual may be said to have passed into the preceding category. In those of the pronounced C type a change will frequently not be observed within ten minutes; in two cases only have I found the condition noted when standing, to be maintained after severe operation. Further, when the muscles in the front of the abdomen are examined, it will be readily determined that no contraction occurs in the rectus abdominis, and that the general tension of the abdomen is greatly decreased.

The muscles of the posterior group, being no longer required for the action of balance, generally pass out of action, but this statement is not so reliable as the preceding, owing to the fact that the patient naturally raises the body, and tends to keep it to some extent so raised, when the examining hand is passed round the loin.

The amount of protrusion of the epigastrium and abdomen generally, when supine, varies considerably. In those patients of the A class, the propulsion is absent, very small, or even reversed. In those of the B and C class, it is considerably greater, and is greater above than below the umbilicus.

While making these observations the opportunity was taken of seeing what actions induced a contraction of the abdominal muscles. It was found that in individuals of class A, raising the head from the pillow did not as a rule produce a contraction of the rectus muscle of the abdomen, but in those of the B and C classes a marked contraction did occur. When raising the shoulders, in each class, the rectus and the lateral muscles gave a firm contraction, and in nearly every individual flexion of the thigh caused a contraction of the rectus abdominis but not always of the lateral muscles.

In the A type during quiet respiration when erect there is little protrusion of the abdomen, and such as is observed is spread equally over the whole area. The lower ribs are slightly everted. In deep inspiration, however, the whole front of the chest rises, the lower ribs evert greatly and are rendered obvious owing to the general retraction of the abdomen. In the C type very different phenomena occur. In quiet respiration when erect the abdomen moves little, such movement consisting in distension of the part below the umbilicus, and where occurring above the umbilicus it is in the neighbourhood of the middle line. In deep inspiration the chest glides upwards, the middle set of ribs bulge laterally, the lower costal margin is not everted and may actually be drawn inwards, the abdomen is protruded generally, such protrusion being accentuated in the epigastrium.

When the supine posture is assumed other marked changes occur. In the A type the chest as a whole moves upwards, the clavicles are not prominent, the lower ribs are everted, there is considerable recession of the epigastrium and hypochondria, so that there appears to be a steep descent from the thorax to the abdomen, which renders the margin of the ribs extremely prominent. In the C type the chest as a whole glides upwards a little, the clavicles remain obvious, the cartilages of the 6th, 7th, and 8th ribs stand out prominently, the abdomen remains at the same level or may become flatter, but does not tend to sag laterally, nor do the flanks bulge outwards. The lower ribs may gradually become everted.

In the A type the changes which accompany quiet respiration are very slight; recession of the lower end of the sternum, the lower ribs evert a little more, the epigastrium is not protruded and may even sink farther backwards, and if distension of the abdomen takes place it is noticed to be spread out mainly below the level of the umbilicus. In the C type the lower ribs do not move outwards and may even be drawn inwards, the chest moves upwards and the

sternum forwards, the middle ribs are pushed outwards, and the epigastrium is protruded.

In the supine posture with deep inspiration in the A type the chest rises somewhat towards the head and increases antero-posteriorly at the level of the joint between the manubrium and the gladiolus. The lower end of the sternum is retracted so that the manubrium is bent on itself, the middle and lower ribs are everted, a greater amount of movement occurring on the right side than on the left. The epigastrium and hypochondria recede still farther, the chest becomes wider and as a whole tends to resemble a cone. The rise of the chest is not so great as in the upright posture. In the C type the chest as a whole moves more towards the head and there is obvious recession of the pre-tracheal region above the manubrium. The sternum as a whole swings forwards, the ribs acting as cranks, the lower end of the sternum is but slightly retracted, the width of the chest opposite the lower end of the sternum is increased, but not that between the twelfth ribs, the abdomen is pushed forwards, notably in the epigastrium.

In both types, when assuming the supine posture, the circumferential measurement of the chest at the level of the nipples shows an increase of approximately half an inch, a similar or greater decrease taking place in the measurement of the girth of the abdomen. In the A type, shortly after lying down, the apex beat rises and can be located in the fourth interspace, a little farther from the sternum than when erect. Similarly the liver dullness at the nipple line will be found to be one space higher than when standing. In the C type these levels are not influenced by the change of posture.

On comparing the breath sounds in the axilla, in the third and sixth spaces respectively, it will be found that inspiratory murmur will be louder at the upper point than at the lower in the A type, but in the C type the intensity at the two points will be equal or reversed.

It will be observed that in the supine posture the upper part of the sternum comes forward a little in the C type, but in the A type there is considerable bending back of the manubrium on the gladiolus.

Types A and C are easily recognized and constitute distinct physiological and pathological groups. A member of the A type, when prepared for examination, nearly always behaves in a characteristic manner. He draws himself up to his full height, slaps his chest, takes a deep breath or yawns, during which his whole chest is thrown forward and raised, his epigastrium falls in. Following this he puts his hands in his pockets and looks bored. Type C comes forward in a timid manner and stands patiently with shoulders bent forward.

The great majority of adults (roughly 95 per cent.) fall into the intermediate or B group with a general tendency towards the A class. Characteristic examples of either the A or C types are accordingly uncommon.

As regards pathological phenomena, type A develops diseases of the lower lobes, such as bronchitis and emphysema. Type C includes cases of visceroptosis and those with poor terminal circulation. Many cases of pulmonary tuberculosis

will be found in the C class, and in the B class when the type tends towards that end of the scale which approximates to the C type. (All pathological chest conditions have been excluded from this part of the investigation.)

This classification originated from differences observed in the behaviour of the muscular contraction occurring in the lateral region of the abdominal wall. Other muscular actions have been investigated, viz. the scaleni, triangularis sterni, and transversalis abdominis. Observations by palpation of the intercostals are not recorded owing to the uncertainty of their responses,—a contraction due to pain or to the tickle reflex often occurring,—and to the impossibility of separating the action of the external from the internal intercostals by this means. The scaleni can be felt in the neck in all. One fasciculus of the triangularis sterni which extends from the xiphisternum to the neighbouring costal margin can be palpated in those individuals in whom the space between the xiphisternum and costal wall is sufficient to admit the tip of the little finger. The important part of the transversalis abdominis is that arising from the costal margins, and therefore lies above a line drawn from the tip of the tenth rib to the umbilicus.

During quiet breathing in the A class the scaleni behave in a varied manner. In the most marked types there is either no contraction, or contraction in expiration; in less marked types some contraction occurs in inspiration. The triangularis sterni may not contract at all when the individual is either lying or standing, but it usually does so when he is lying, and it is then expiratory in function. No doubt this muscle is important in drawing down the ribs in expiration. It is obvious that the expiratory inversion of the upper ribs is a muscular act, because this action takes place in a peculiar way which is similar in character to that occurring in the lateral group of muscles. It is probable that the fibres lying deep to the sternum which cannot be palpated are expiratory in action and serve to draw down the upper ribs in expiration. The transversalis abdominis does not contract.

In the C type the scaleni are inspiratory. The triangularis sterni and transversalis abdominis are also inspiratory. The contraction is stronger when erect than when supine. Different sections of the latter muscle can be distinguished, viz. that part between and above the eighth costal cartilages, the portion on a level with the ninth costal cartilages, and the remainder between the former and the line drawn between the tenth costal cartilages and the umbilicus.

In the B or intermediate class the muscles behave in a manner in accordance with the general resemblance of the chest to the A or C type. In some of the B cases there is a slight difference in the action of the transversalis abdominis on the two sides. On the right side this muscle may contract late in the inspiratory phase, thus acting as a check on the right costal margin, which therefore does not evert as much as the left, where no similar contraction can be detected. As a result of this action of the muscle, a slightly increased tone is experienced in the right half of the epigastrium. It is more noticeable when supine than when erect.

With regard to measurements of the chest—these have on the whole been disappointing, and give little information even when correlated. The diameters estimated by Woods Hutcheson (15) have not in my hands been of great value. Generally speaking, there is an increase in all diameters whether transverse or antero-posterior on assuming the supine posture, and the variations are of proportionate degree in the A and C type except in the following points. (1) An antero-posterior diameter taken from the manubrio-gladiolus joint at right angles to the long axis of the body will show a greater increase in the A than in the C type on assuming the supine posture. (2) A transverse diameter taken at the level of the lowest ribs in the mid-axillary line will increase on assuming the supine posture immediately and to its maximum in the A type, but slowly in the C type. In the latter, twenty-four hours after assuming the supine posture, it may be found to be one or two inches greater than when erect, and one to one and a half inches greater than when taken ten minutes after lying down. This supports the statement that all individuals, even the C type, tend towards the A type when lying supine for any considerable period. This diameter is considerably smaller in the C than in the A type. (3) The measurement which shows least variation in the same person in different postures is one taken from the supra-sternal notch, to the lower border of the lowest rib in the mid-axillary line. It is relatively longer in the C than in the A type—roughly in proportion of seven to six, taking the height of the individual as the unit for comparison.

More satisfactory than measurements is the general view of the chest, regarding it as consisting of an upper and lower half. The A type will have a well-developed upper half and a broad lower half with a broad sternum somewhat depressed and a prominent xiphisternum; the depth will vary. As a whole the chest will appear short in proportion to the height. The C type is badly developed both above and below; the sternum long, and easily palpated with finger and thumb; the rib cartilages slope towards the pelvis. The xiphisternum is deep and lies behind the costal cartilages, which almost meet in the middle line. The chest appears long and cylindrical. The B type is a compound of these two types, and may be well developed in the upper half and badly in the lower, or the converse, or may be an average of the A and C types throughout.

It was next decided to investigate these types by means of the X rays, with the object of observing the movements of the diaphragm.

It is obvious that in dealing with X rays we are dealing with shadows cast by objects opaque to these rays, otherwise a silhouette. Accordingly, the results never can be absolutely accurate, unless it is possible to work with the source of light, the screen, and the patient in constant relationship. As far as possible this has been done. It is estimated that in the tracings one-sixth of the changes recorded must be discounted as resulting from magnification. In order to obtain a level it was necessary to get fixed points wherewith to estimate differences during the postures selected for investigation. Lead crosses and lines were stitched to a thin elastic band, which was then placed round the patient's chest. It was not possible to fix them at predetermined points both back and front,

owing to the fact that when lying down the anterior wall of the chest rises in a varying degree relatively to the posterior. One of the crosses was always placed approximately over the nipple in the male subject, and as near as possible on the fourth space in the female. The line was then arranged posteriorly in such a position that a plane could be obtained, in which would lie the source of light and the anterior and posterior opaque objects, both in the standing and supine postures. In the standing position it was found that the posterior

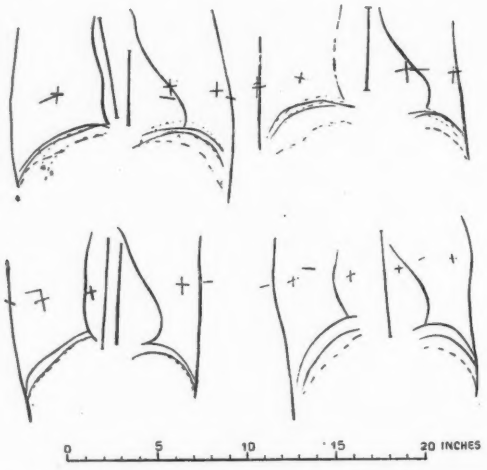


FIG. 3. X-ray tracing of an A type (upper line) and of C type (lower line).

In each instance the diagram to the left represents standing, that on the right lying supine. The continuous line represents inspiration and expiration of a quiet nature. The lowest broken line in each instance represents the position of the diaphragm in deep inspiration. The small broken line in the A type shows the effect of pressure applied to the lateral chest-wall. In both the A and the C types with deep respiration the descent of the diaphragm is greater when supine than when standing. In the A type it is greater than in the C type, and this is especially to be noted in the upright position. The C type when standing shows practically no descent. The rise of the level of the diaphragm is notable in the A, not in the C type, when the supine position is assumed. The lack of descent below the right border of the heart is also noteworthy, occurring in the C but not in the A type. This limitation would appear to be due to the pericardial ligament which partially envelops the inferior vena cava and is sufficiently inelastic as to prevent extension. There is nothing to correspond to this structure on the left side. However, the action of the left crus, as judged by the arrangement of its tendinous attachment, is largely on this pericardial ligament. There are certain differences of outline of the diaphragm in the two types, but with deep inspiration these differences largely disappear. The movement of the visible diaphragm is greater in the C than in the A type during quiet respiration. Lateral pressure in the A type produces a diaphragm showing greater resemblance to the C type than when such is not applied.

marks had to be placed at a higher level than the anterior, in order to allow for the changes subsequent to the supine posture. Where the lines and crosses in the diagram are not in the same plane, a fixed point can be found by taking a point an equal distance from the levels of the lines and crosses; this will allow comparative measurements of the height of the diaphragm to be made. It was also necessary to see that there was a fair amount of correspondence between the highest position of the diaphragm in both postures, relative to the anterior and posterior walls of the chest. Fortunately, the highest point of the diaphragm

either standing or lying is approximately the same. This observation was made by taking the tracings on an axis through the chest from side to side. Except where otherwise stated, the light was at the back of the patient and the screen in front.

In reference to the methods of recording what is seen, I have deliberately chosen tracings rather than negatives. Photographs are easy to obtain where maximum inspiration and expiration are to be recorded. The essence of these observations, however, was to record what happened in quiet respiration, and it is obviously impossible to ask the patients to stop breathing for a few seconds when they are supposedly breathing unconsciously. The results obtained with the photographs attempted were not at all in accordance with what had been seen on the screen. Therefore the method employed was to get the patient to stand or lie quite comfortably, and then to make a tracing with a grease pencil on the screen, subsequently transferring it to the tracing paper, which at a later period was finished by putting in the lines more distinctly. This is a convenient method and on the whole fairly accurate. All the actual work in taking the tracings, except in one instance, was done by Sergeant Forder, the chief assistant of the X-ray department at King's College Hospital, to whom I express my indebtedness.

It has also not been considered of much value to give exact measurements of the variations, because there is admittedly a constant magnification which varies according to the antero-posterior diameter of the individual, and the distance between the chest and screen, when the person is standing comfortably, and when supine. A number of tracings were taken in various positions, and eventually it appeared that the most valuable ones for the purpose of this investigation were obtained with the screen in front and the light behind the individual in the following positions: standing comfortably, or lying on the back with the head supported by a pillow.

Comparing the supine with the erect posture, it is noticeable that in nearly every instance the level of the diaphragm rises immediately. It ascends with gradually increasing expirations, and the succeeding inspirations are on a lower level than the preceding ones. If at any time the patient takes a voluntary or unconscious deep breath, the diaphragm will descend and will gradually resume the position from which the descent was made, in successive stages as indicated above. The amount of ascent will vary considerably. The ascent is not the same on both sides, but is usually greater on the right. A small amount of change occurs in the curvature of the diaphragm as estimated, from one chest-wall to the other. It tends to become flatter when the supine posture is assumed, there may be a slight dip towards the subpericardial region, and the variation of the inspiratory and expiratory lines is a little greater in this area than nearer the costal margins. I have not been able to obtain records of the patient lying quiet for a longer period than ten minutes. The records of this time showed that the diaphragm was sometimes higher than at the end of about a minute. Sometimes, on the other hand, it was a little lower.

In the A class on assuming the supine posture an immediate rise in the level

of the diaphragm takes place, which varies from $\frac{3}{4}$ to $1\frac{3}{4}$ inches on the right side and from $\frac{1}{2}$ to $1\frac{1}{4}$ inches on the left. In the C class the rise on the right side is from 0 to $\frac{1}{4}$ inch and on the left from $\frac{1}{8}$ to $\frac{1}{2}$ an inch. The rise on the right side is greater than that on the left in the A class, but nearly always less in the C class. In the C class the diaphragm is more oblique than in the A class, and generally the curves of inspiration and expiration show greater resemblances for the two postures in the C class than in the A group.

I have made two further investigations; after recording the height of the diaphragm both in inspiration and expiration during quiet breathing I have asked the patient to take as deep a breath as possible and noted the maximum descent of the diaphragm. In the A class when erect the descent is considerable, and when supine, after the initial rise, the descent of the visible diaphragm is very much greater even than that in the standing posture; whereas in the C type the descent in both postures is less than that in the A type, and when standing is quite insignificant; it is moderate when supine. There is thus a greater 'reserve' in both types when supine than when erect, but in the A type it is much greater in either posture than in the C type. The movement upwards of the chest has been discounted.

The second investigation was made with a view of mapping out in the greatest possible detail the angle where the diaphragm leaves the ribs, and this in quiet and deep respiration in both postures. It will be observed (see Fig. 4) that the angle is more obtuse in the A class when lying than when standing in quiet respiration, but with a deep inspiration is practically the same in either posture. In the C class the angle is almost identical in both the upright and supine postures under the varying conditions. It is thus seen that in the C class the shape and level of the diaphragm are almost identical in the two postures and under all circumstances, whereas considerable variation as well as a rise in level occurs in the A class when assuming the supine posture. This indicates that the visible part of the diaphragm alters in the A type, but is contracting in a similar manner in the C type in the two postures selected.

As to how these results are to be explained is a matter of some difficulty. The diaphragm has, amongst other things, been compared to the nozzle of a piston which rises and falls in the chest, which is thus likened to the barrel of a syringe. It is to be noted that the parts of the diaphragm seen under the X-rays are those parts which lie between the outer margins of the pericardium and chest-wall on either side. Only occasionally, and then under circumstances of forced inspiration, can any considerable portion of the sub-pericardial region be seen. We must therefore assume that we are dealing with that part of the diaphragm which stretches between its origin in the mid-axillary line and the pericardium as situated in that plane. A rounding off of the piston-head towards the costal margins will represent a contraction by that part of the muscle which lies in the mid-axillary plane, whereas a flattening of the upper level of the diaphragm would suggest a relaxation of the same parts. The diaphragm with rounded costal margins is usually found in the

C class both standing and lying. The flatter surface is characteristic of the A class, especially when supine. The fact that in deep inspiration both classes show a rounded costal margin seems to favour this conception, for it may be assumed that then every fibre in the diaphragm will be thrown into contraction. It would also, however, suggest that when, in the supine posture, in the A class flattening of the upper surfaces of the diaphragm takes place, this is due to some mechanism other than the contraction of the costal fibres in the mid-axillary plane; and a slight degree of increased contraction on approaching the subpericardial area, would suggest that such a contraction is produced in some part of the diaphragm which lies nearer to the mid-plane of the body.

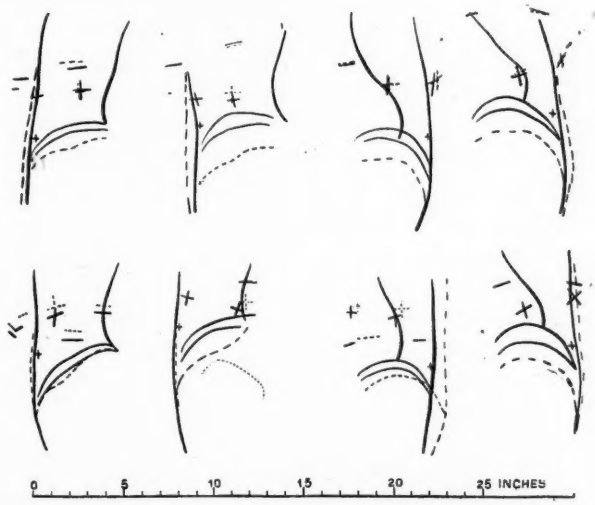


FIG. 4. X-ray tracings from the same individuals as Fig. 3, but with the tube focused over the costo-phrenic angle as indicated by star.

Upper row A type, lower row C type. Reading from left to right they are arranged as follows: (1) right side standing, (2) right side lying, (3) left side standing, (4) left side lying. Continuous line is quiet respiration, inspiration and expiration. Broken line forced inspiration.

The 'reserve' is in every instance greater when lying than when standing, and greater in the A than in the C type. In A 2 the asymmetry of the continuous lines is noteworthy, and in C 2 the fixation of the subcardial extremity. In C 3 and C 4 the depression of the forced inspiratory curve below the heart is more marked than in the corresponding figures of the A type.

If we then correlate the afore-mentioned points we find that there are two types of quiet breathing which can be picked out from a number of cases investigated promiscuously. The characteristics of that class which I have designated the A type are: the chest is relatively short and wide, it is also relatively deep, especially at the level of the lower end of the sternum. There is considerable expansion of the lower part of the chest. The lateral abdominal muscles do not contract, nor is there any tone during expiration, whether lying or standing. None of the other three muscles investigated contract in inspiration, but the triangularis sterni may contract in expiration, as may the

scalene group. When lying on the back there is little propulsion of the epigastrium but considerable inspiratory recession of the lower end of the sternum with eversion of the middle ribs, and where possible of the lower ribs also (i. e. in the young, where greater movement of ribs occurs owing to greater pliancy). On X-ray examination the diaphragm ascends in the thorax and its upper surface becomes flattened.

In the C type the chest is relatively long, narrow, and shallow anteroposteriorly. There is little eversion of the lower ribs; the lateral abdominal muscles lend considerable support to the abdomen, both by a general tone during inspiration and expiration and by forcible contraction during expiration. The scaleni, triangularis sterni, and transversalis abdominis contract in inspiration. On lying down there is considerable epigastric propulsion and the chest tends to move up and down without altering its diameters to any degree. By the X-rays it is seen that the diaphragm does not rise to any extent, and its upper surface remains similar to what it was in the standing posture.

The investigations with the X-rays show that in the B class in the supine position the diaphragm rises and tends to become flatter, but not in the same degree or at the same rate as in the A type. The X-ray results, therefore, fall into line with the general conclusion drawn from measurements, &c., that all persons tend to the A type when lying down.

It may therefore be stated that from a series of individuals two types can be separated at opposite ends of the scale. In quiet respiration these two types show differences of form, of associated muscular contraction, of movement, and variations in the behaviour of the diaphragm, both when standing and on assuming the supine posture. The A type breathes in one manner, the C type in another. With prolonged recumbency the C type tends to assume the mechanism exhibited by the A type. The last part of this statement, which is emphasized later, is made on the evidence afforded by measurements, &c., conjoined with changes which X-ray examination show to occur in those members of the B type who approximate to the C type. In these when supine the diaphragm rises slowly, and at the end of ten minutes is but slightly higher than when observed immediately after lying down.

The B type is a compound of the A and C types with a general trend towards the A type when supine and towards the C type when erect.

Comparison of the different types.

In the high paraplegia the muscle of inspiration is essentially the diaphragm, but the costal portion is under a disadvantage owing to the interruption in the spinal cord severing the connexion between the central respiratory mechanism and the intercostal nerves which, uncertain though their importance may be in man, pass through this portion of the muscle. The crura, not receiving a nerve supply from this source, do not labour under such a disability.

In diphtheritic paralysis of the diaphragm the assumption is that the diaphragm

is inoperative. In the A type the diaphragm is presumably normal, as also in the C type. In the first three conditions, high paraplegia, diaphragmatic paralysis of diphtheria, and in the A type, there is no tone of the abdominal muscles, there is sinking in of the epigastrium amounting in some cases to actual inspiratory recession, there is inspiratory recession of the lower end of the sternum and eversion of the lower ribs greater on the right than on the left side. In the C type, on the other hand, there is protrusion of the epigastrium with raising of the chest as a whole, and inspiratory and expiratory tone or contraction in the different abdominal muscles. The lower end of the sternum does not (or only to a very slight degree, and then not immediately on assuming the supine posture) recede during inspiration.

In these several conditions we find (1) in the high paraplegia very complete deflation of the lower lobes of the lung, (2) in the diaphragmatic paralysis of diphtheria a complete deflation with oedema or congestion, (3) in the A type marked tendency to deflation when maintaining the supine posture, and (4) in the C type less evidence of considerable deflation.

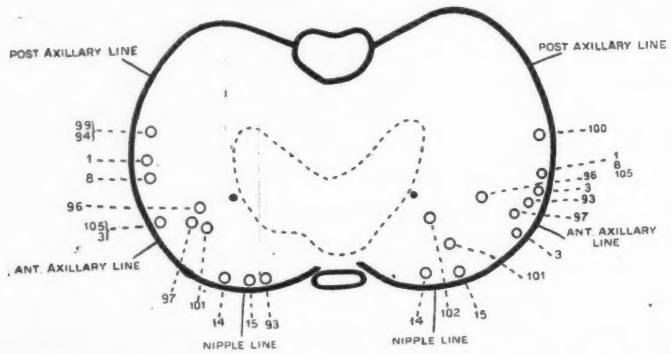
It will be recalled that in the series of thirty cases examined after operation, eleven showed evidence of deflation of the lower lobes. The distinguishing feature was the lack of tone in the lateral abdominal muscles, one of the characteristics of the A type and most of the B type when supine. Deflation of the lower lobes of the lung seems to be clearly connected with that condition in which there is no tone or contraction exhibited by the abdominal muscles.

As the question of lower lobe deflation seemed to be of importance even in the normal individual when supine, observations were made to determine the post-mortem position of the various lobes (Fig. 5).

Several of these cases were typical of the C type, as judged by the shape of the chest, and in one of the most characteristic, the lower lobes were bound down to the diaphragm in a line posterior to the phrenic nerve, but were not deflated. It is therefore certain that a great tendency to deflation of the lower lobes exists whenever any one, even of the C type, remains supine, and the lobes may become fixed in this position by adhesions in inflammatory conditions. Deflation should be regarded as a normal sequence of this posture with such conditions as entail quiet breathing.

That deflation of the lower lobes should occur as a result of assuming the supine posture with quiet breathing, but without what Pasteur describes as 'collapse attacks', or without paralysis of the diaphragm, may at first sight appear incredible; it will, however, be found in nearly all cases where these conditions obtain, if examination of the back is made in routine manner. Directly the patient recovers, and movements of the head, legs, &c., induce considerable contraction of the abdominal muscles, the signs of deflation will rapidly disappear. Pasteur has estimated that deflation occurs within 48 hours of operation, and it is during this period that the 'collapse attacks' frequently occur. My observations agree with this time limit as applied to quiet breathing in the supine posture. A few deep breaths are sufficient to expand the lower lobes.

While, therefore, a period of 24–48 hours is necessary for the production of deflation, a few seconds only are required to remove all traces of the condition. It is obvious that where pain prevents a free contraction of the muscles of one or both sides of the abdomen, contraction will be inhibited and the lower lobe or lobes will remain deflated. Hence the side on which the surgical incision is made will tend to be quiescent on account of the pain produced by contraction, and accordingly deflation will tend to be more marked and to persist longer on this side. This



× 93 (23) Br.-pneumonia. Left lung solid. Rt. affected slightly. Upper lobes 1 in. apart.

× 94 (16) Influenza. Rt. and Lt. lower solid. Lt. upper 1½ in. from mid-line.

96 (6) Tub. meningitis. Adhesion Rt. upper. Rt. and Lt. upper 1 in. apart.

× 97 (2) Tracheal diphtheria. Upper lobes 1½ in. apart.

99 (16) Empyema. Upper and lower. Rt. upper br.-pneumonia.

100 (78) Malignant oesophagus. Adhesions Rt. *lower*.

× 101 (50) G. P. I. Fit.

102 (10/12) Br.-pneumonia Rt. Adhesions Rt. upper.

× 105 (57) Suprarenal haemorrhage.

× 1 (2½) Laryngeal obstruction. Upper lobes 2½ in. apart.

3 (15) Spinal caries. Lt. lower lobe fixed by adhesions.

8 (20) Cancer uterus. Both upper and lower lobes fixed by adhesions.

× 14 (39) Unexpected death. Malignant oesophagus. Artificial resp. 20 min.

× 15 (63) Emphysema and heart failure. Sudden death in street.

× indicates absence of adhesions on either side.

The numbers in the brackets give the age of the subject.

FIG. 5. Diagrammatic representation of the surface of the diaphragm as seen from above.

The circles represent the position in which the tip of the lower lobe was actually found. Unless it is otherwise stated the internal margins of the upper lobes were found to approximate.

It will be seen that the tip of the lower lobe was found in the recognized anatomical position in three cases only. In one of these death had occurred suddenly, in the second artificial respiration had been performed, in the third broncho-pneumonia was present affecting both lower lobes. In all the other cases the lower lobes were retracted, and in two instances were fixed in this position by adhesions. The inference to be drawn is that there is a natural tendency to deflation of the lower lobes in quiet breathing generally, and in that preceding dissolution. It is further to be noted that the last gasps are constantly of an exaggerated form of the A type of breathing.

(The trachea was obstructed in each instance at the commencement of the P.M. section.)

failure of the lower lobe to expand may persist for weeks or even months after a 'collapse attack', or after pleurisy or empyema, and be followed eventually by recovery. Indeed, I have seen several cases where the patient has been walking about with signs of deflation in both lower lobes; *vide infra*.

During the course of this investigation a woman of 52 years of age was admitted to hospital, and hysterectomy for uterine fibroids was performed. She

was examined prior to this operation and was found to be of a mixed or B type strongly inclining to the A type. She was seen on the second day after operation and both lower lobes were found to be deflated. She then had the typical signs and muscular reactions of one of the A type. On the following day before dinner she felt faint, became cyanosed, and died quietly without a struggle in the course of half an hour. At the post-mortem a thrombus 15 inches long, and bent on itself, was found fixed in the orifice of the pulmonary artery. The upper and middle lobes on the right side and upper lobe on the left side were over-distended and crepitant. No adhesions were found between the chest-wall or diaphragm and the lungs, no fluid was found in the pleural cavity, and no trace of recent pleurisy or pericarditis was discovered. The intralobar fissure on the left side was universally obliterated and could not be opened up, and on the right side a firm adhesion one inch in width was present between the middle and lower lobes at a point four inches from the anterior border of the lung. Except in the region of the fissures both lower lobes were deflated, slaty-blue, airless, and sank in water. On the left side in the neighbourhood of the fissure, the lower lobe in an area extending for one inch parallel to the fissure was crepitant and of normal appearance; on the right side the lower lobe revealed a similar condition to that of the left side, except that the non-deflated area was in the shape of half an ellipse, the greatest diameter being four inches and the lesser half diameter 1¼ inches in the region of the adhesion (Fig. 6, Plate 8). The right lung was retained as a permanent specimen. The bronchi of the left lung were cut open with a fine-pointed pair of scissors and no difference was found between the bronchial tubes of the deflated and non-deflated portions of the lung. A small quantity of brown material, lying on the dependent surface of the bronchi, in either case proved by microscopic examination to be desquamated cells from the wall of the bronchus with a little coagulated serum. No intrabronchial obstruction was found in any of the bronchial tubes. This specimen is a rare one of its kind. Clinically, it was an ordinary case of postural deflation. The cause of death from embolus was clear, and there was no sign of 'collapse attack' before death. The post-mortem findings in this case are also strongly against the theory put forward by Elliot and Dingley that deflation is due to obstruction in the bronchial tubes by mucus.

The lungs, after removal from the body, were submitted to Dr. Knox for X-ray examination. No difference was detected between the upper (inflated) and the lower (deflated) by this means. A similar result was recorded in the preserved specimen from a case of high paraplegia.

It is from the high paraplegia and diphtheritic paralysis of the diaphragm and the A type that an explanation must be sought. Before proceeding farther, however, I shall make some observations on the question of diphtheritic paralysis. These cases are rare, and becoming still more so owing to the use of anti-diphtheritic serum, and it is but seldom that diaphragmatic paralysis arises in other diseases. A boy of 10 years of age was admitted into King's College Hospital in the early part of 1914 with multiple neuritis of obscure origin.

Paralysis of the diaphragm was diagnosed by the neurologist on the grounds of epigastric recession, marked eversion of the lower ribs with inspiration, and difficulty in making expulsive efforts in which the musculature of the abdomen was concerned. When examining the patient I found that the abdominal wall was quite toneless, and in addition to the eversion of the chest-wall a definite Harrison's sulcus was produced with each inspiration. The inspiratory recession of the epigastrium was quite marked, as was the lower sternal recession. With the object of investigating the phenomenon I placed one hand on each side of the lower thorax in the mid-axillary line, and proceeded to make gentle pressure, and was surprised to observe that the epigastrium, which had become level owing to the pressure, then began to come forward with each inspiration in the normal way. The boy, who was quite intelligent and not actually ill, felt relief by this procedure. The breathing resumed the former character when the support was withdrawn. On X-ray examination it was found that the visible diaphragm was high up in the chest and showed very little movement, but when the lateral pressure was applied, it was seen that the visible portion of the diaphragm commenced descending, and the descent increased in excursion with succeeding inspirations. On relaxing the support the diaphragm was seen to resume gradually its original form and position.

Since that time I have had the opportunity of producing this pressure phenomenon in six cases in which the same signs were present. Unfortunately, I have had no opportunity of examining all these cases by X-rays, and have only one tracing of this condition to produce. In these cases typical epigastric recession, with retraction of the lower sternum and eversion of the lower ribs, was present during inspiration; this recession was changed into propulsion and the other signs obliterated by the means already described. Five were cases of severe diphtheria seen at the North Eastern Hospital, the sixth case was that of a child brought to King's College Hospital with an intracranial tumour. The child lay quiet, only breathing eight to ten times in the minute; the chest was cone-shaped, the lower ribs everted, and the whole of the upper part of the abdomen receded upwards into the chest with inspiration. X-ray tracings showed on the left side no movement of the diaphragm during inspiration, on the right side considerable movement, the result of which was to obliterate the crescentic shape of the diaphragm. In this case, on supporting the sides of the chest, the lines of inspiration and expiration on both sides became almost parallel, and the left half of the diaphragm commenced contracting. On increasing the pressure the descent of the diaphragm was very great, but so suddenly carried out that it was impossible to obtain a satisfactory tracing (Fig. 7).

In a case of chorea the respiratory mechanism was affected. For four or five breaths there would be epigastric recession during inspiration; then followed an inspiration in which there was marked epigastric protrusion. By the X-rays it was seen that in the former method of breathing little movement occurred, but in the latter a marked descent of the visible diaphragm was observed.

Pressure made in a similar manner on the chest of normal individuals in the

supine posture will produce an almost similar effect. The patient is instructed to take no notice of what is being done, but to look at the ceiling and think of something pleasant. By pressing the lateral thorax in a downward and inward direction, it is first noticed that the epigastrium rises to the level of the costal margin; it pauses there for a few seconds, during which time there is much resistance to the pressure of the chest-wall, and a sensation is conveyed to the hand very much like, but an exaggeration of, that received from an eighth-month foetus which has been disturbed in the process of abdominal examination of the mother. After the period of quiescence (about 20 seconds) gradually increasing waves of propulsion in the epigastrium are produced, resembling those normally seen in the C type when lying down. Simultaneously

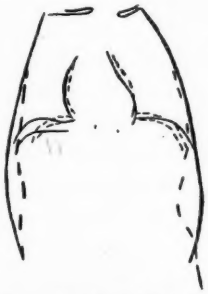


FIG. 7. X-ray tracing of the diaphragm of a child of four years exhibiting the signs of 'diaphragmatic paralysis'.

The continuous line indicates the condition prior to lateral costal pressure, the results following this pressure are shown by the interrupted line.

In the first instance there is no inspiratory descent of the left side and the movements in inspiration and expiration of the right side are not symmetrical. Lateral pressure causes a rise of the diaphragm in the region of the pericardium and promotes an inspiratory descent of the left side. The lines indicating inspiration and expiration are symmetrical.

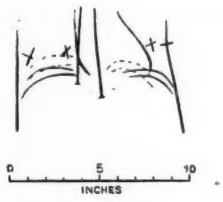


FIG. 8. X-ray tracing in a normal child of ten years of age, showing the effect of lateral costal pressure. The diaphragm rises notably near the middle line.

the resistance to the pressure of the hand diminishes and further struggling is not experienced. This manipulation produces no striking change in the C type, is easy to produce in most of the B class, and can generally be developed in the A class, but with great difficulty or not at all in the most marked cases. In a case of high paraplegia this lateral chest-pressure produced so much discomfort that the attempt had to be abandoned.

In a patient of the B class submitted to this procedure under the X-rays very little difference is observable, except that there is a slight rise of the diaphragm in the subpericardial region, and the costo-phrenic angle becomes more acute. When the C type of breathing is developed by chest-pressure no tone or contraction is detected in any of the abdominal muscles, and on relinquishing the pressure the original conditions ensue (Fig. 8).

This phenomenon of changing one type of respiration into the other is of great importance. It is obvious that some very marked change is taking place when lateral costal pressure is being made, as instanced by the transient quiescence in the epigastrium, the resistance to the pressing hands on the chest, and when this is overcome the change from epigastric recession to protrusion. It shows that in ordinary respiration we have to deal with two distinct mechanisms in the A and C types which may be made to alternate as in the pressure observations, or exist contemporaneously as is the case in the B or intermediate type. The next problem was to differentiate between the two mechanisms.

The A type, occurring as it does in the more primitive conditions—psychic stimuli, &c.—seems to offer possibilities of a solution which are not so readily to hand in the C type. No explanation can be satisfactory which does not take into account the following phenomena: (1) lower sternal recession, (2) eversion of the ribs, greater on the right than on the left, (3) sinking in of the epigastrium.

FIG. 9. X-ray tracing from a case of paraplegia resulting from a lesion of the third dorsal segment.

The continuous lines show natural inspiration and expiration and are not symmetrical; the movement is deficient at the costal wall.

The broken line shows the descent accompanying a maximum voluntary inspiration. The difference between the former and the latter indicates the 'reserve' present in these cases.

It seems probable that we are dealing with the same type of condition in the high paraplegia, in the so-called paralysis of the diaphragm, and in the normal individual of the A type in the supine posture, but that in the two former the condition is much more marked.

In diphtheritic paralysis of the diaphragm lateral costal pressure produces the same effect as in the A or B types, i. e. it results in the C type of breathing, but the greater response suggests greater initial relaxation of the costal fibres of the diaphragm. In the A type of individual when assuming the supine posture, the diaphragm rises and has a considerable reserve capacity for voluntary inspiration. The same form of reserve, but with a still greater capacity, is present in the individual with a lesion high up in the dorsal spinal cord, and apparently the diaphragm is high in the chest in both high paraplegia and diphtheritic paralysis, as judged by the marked reserve of contraction (Fig. 9). (It will be recalled that the reserve is present in the A type to a much greater extent than in the C type.) In these three classes of patients all the abdominal muscles are completely toneless (this being a characteristic difference between a lesion high up in the dorsal cord and one which is low down. In the latter case, as is well known, the abdominal muscles are hypertonic.) In the paralysis high up in the

dorsal cord practically the only muscle of inspiration is the diaphragm; being supplied through the phrenic nerve. The lower costal nerves which to a small extent probably supply the costal portion of the diaphragm are separated from the respiratory centre. The costal portion of the diaphragm must labour under considerable disadvantages, in that part of its nerve supply is cut off; the crural portion of the diaphragm which is supplied by the phrenic nerve only will not suffer in any such degree.[2] A more probable explanation is that in quiet respiration sufficient aeration is attained without necessitating a full contraction of the diaphragm.

In the normal and diphtheritic person the pressure phenomena described above and the observations under the X-rays demonstrate that the costal portion can be induced to contract, but actually is in abeyance. It is impossible to assume on experimental or clinical grounds that the whole of the diaphragm is paralysed in so-called diphtheritic paralysis, but it is equally clear that the visible portion of the diaphragm cannot be seen to contract on X-ray examination. The obvious deduction, therefore, is that it is the part of the diaphragm not visible to the X-rays which is contracting, in other words, the crura. It is reasonable to assume that in high paraplegia the crural part of the diaphragm would be far less affected than the costal portion and would act strongly. Strong action of the crural portion of the diaphragm in an antero-posterior direction would seem to supply the best explanation of the lower sternal recession which occurs in inspiration, and which has hitherto generally been attributed to the obstruction of air entry into the lungs. The similarity in the functional activity of the diaphragm in diphtheritic paralysis and in the A type would suggest the same explanation, viz. diminished contraction or tone in the costal fibres and strong action of the crura.

In diphtheritic paralysis of the diaphragm attention has been attracted to the inspiratory eversion of the lower ribs, which is always greater on the right than on the left side, and for which no satisfactory explanation has been put forward. A similar eversion occurs in the high paraplegic and in the A type when supine. This rib movement may also be explained as the result of the action of the diaphragm in an antero-posterior direction, which (if this part alone were acting) would tend in the course of its contraction to pull backwards the 7th and 8th costal cartilages of either side, and so evert the lower ribs, to pull down that part of the liver which lies in the medial plane, and rotate the greater mass of this organ outwards, i. e. to the right,—always assuming that the fibres of the diaphragm arising from the lateral chest-wall are not acting. It should be remembered also that the pillar of the right crus is better developed than the left, and could thus produce a more marked effect on the ribs of the right side.[3]

[2] In animals the marginal portion of the diaphragm at its costal origin does not degenerate when the phrenic nerve is cut, and it must be assumed that this result is due to its costal supply.

[3] The diaphragm is not actually attached at all firmly to the back of the sternum. The firmer attachment anteriorly is to the seventh and adjacent ribs and cartilages by means of

Coincidently with the widening of the epigastric angle and the eversion of the ribs, there would be a tendency for the epigastrium to be pulled back, by means of the firm subperitoneal connexions, and to fall in, owing to the increase of space immediately below the diaphragm, again providing that the remainder of the diaphragm and the muscles of this part of the abdominal wall are in a lax condition and offering little resistance.

In the body of a person recently dead, pressure on the lower part of the sternum, reproducing an antero-posterior pull of the diaphragm, produces an eversion of the upper part, and to some extent of the lower part of the chest, with raising of the upper five ribs. This is not so great a movement as in the living, where probably other muscles (the intercostals ?) assist.

We are justified in assuming that retraction of the lower portion of the sternum, lack of protrusion of the epigastrium in inspiration, elevation of the middle and upper ribs, eversion of the lower costal margins, inflation of the upper lobes, and deflation of the lower lobes are signs indicating contraction of the crura alone.

Accepting the contraction of the crura as explaining the phenomena of inspiration exhibited in high paraplegia, in so-called paralysis of the diaphragm, and in the A type—the costal portion remaining passive—it follows that the alternate phenomena as exemplified by the results of costal pressure and the C type are to be attributed to the action of the costal portion of the diaphragm. This view is strongly supported by the X-ray examination, which shows an almost negligible reserve in the visible diaphragm when an individual of this type is required to take a deep breath while standing before the screen, indicating that he is using constantly the visible or costal part of the muscle.

These two types correspond roughly to 'thoracic' and 'abdominal' breathing, but the terms 'crural' and 'parietal'—referring to the muscular origin of the diaphragm—define the mechanism in a much clearer manner. The parietal form of breathing will frequently be confused with the crural if the upper part of the thorax only be considered. In the crural type there is a small degree of flexion in the manubrio-gladiolar joint but without any considerable raising of the sternum; but in the parietal form there is no alteration in this joint, which is poorly developed or even absent, the chest rises as a whole, and there is recession of the supra-sternal notch. In either case the region of the second and third ribs lateral to the sternum will come forward in inspiration, but by a different mechanism.

the subperitoneal and subpleural fibrous tissue. The lower end of the sternum is retracted by this action of the diaphragm on these parts.

If the central tendon of the diaphragm is dried, the bundles of connective tissue can be seen running from the attachment of the crura on either side of the central portion of the pericardium, and spreading out towards the anterior part of the chest-wall in the regions indicated above.

Confirmatory Evidence.

Embryologically (16), there is a definite distinction in the development of those portions of the diaphragm which rise from the spine and arcuate ligaments, and the portion which takes its origin from the ribs and sternum. The latter is developed from a portion of the longitudinal muscular sheet from which the rectus is derived. The posterior portion is derived from the transversalis sheet which encircles the viscera. Anatomically, there is a definite line of demarcation between these portions of the muscle, and where a fault occurs in the diaphragm resulting in a protrusion of the peritoneum and the formation of a diaphragmatic hernia, it is most commonly found along this line. There is a difference in the amount of muscular tissue found in these parts. Although in man there is a greater weight of muscular fibre in the costal portion of the muscle, yet the greater aggregation of muscle fibre is in the crura, a condition which is even more marked in the rabbit, with the exception that in this animal there is a greater development of that portion (costal) which arises from the sternum and xiphisternum. (The action of this part of the diaphragm must be very similar to that of the crura.) It is also worthy of note that there is considerable decussation of the right and left pillars of the crura, indicating community of action.

The arterial supply of the two portions of the diaphragm is quite distinct. The crura are supplied direct from the aorta, the costal portion from the comes nervi phrenici, a branch of the internal mammary, and from twigs proceeding from the lower six intercostal arteries.

The phrenic nerve divides to supply the crural and costal parts, and whilst it is the sole nerve to the former, the costal portion is stated to receive twigs from the lower five or six intercostal nerves in varying proportions.

An examination of the sternum and the muscles of its posterior aspect shows differences in these two types. The triangularis sterni is well developed in the crural type, the muscle extends to the first and second ribs, the sternum is short and broad and sometimes recurved, and the joint between the manubrium and the gladiolus is well developed. In the parietal type the muscle is only represented by a few fibres running from the sternum and xiphisternum to the fifth and sixth ribs or cartilages; the sternum is thin, narrow, and the joint between the manubrium and the gladiolus is small, ill developed, or even absent. Miss Freeman has dissected a number of sterna from the post-mortem room at King's College Hospital, of which she has depicted three, one of the crural, one of the parietal type, and one of the intermediate or B type (Fig. 10).

The attempt I have made to divide these portions of the muscle may be considered as physiological or functional. The conception I have of the action of the diaphragm is that the crura are the essential portions and are continually acting, both in quiet and in deep respiration, and in all postures, especially the supine, but their action is relatively greater, and almost exclusive in the A or crural type: relatively less in the C or parietal type of chest, especially when

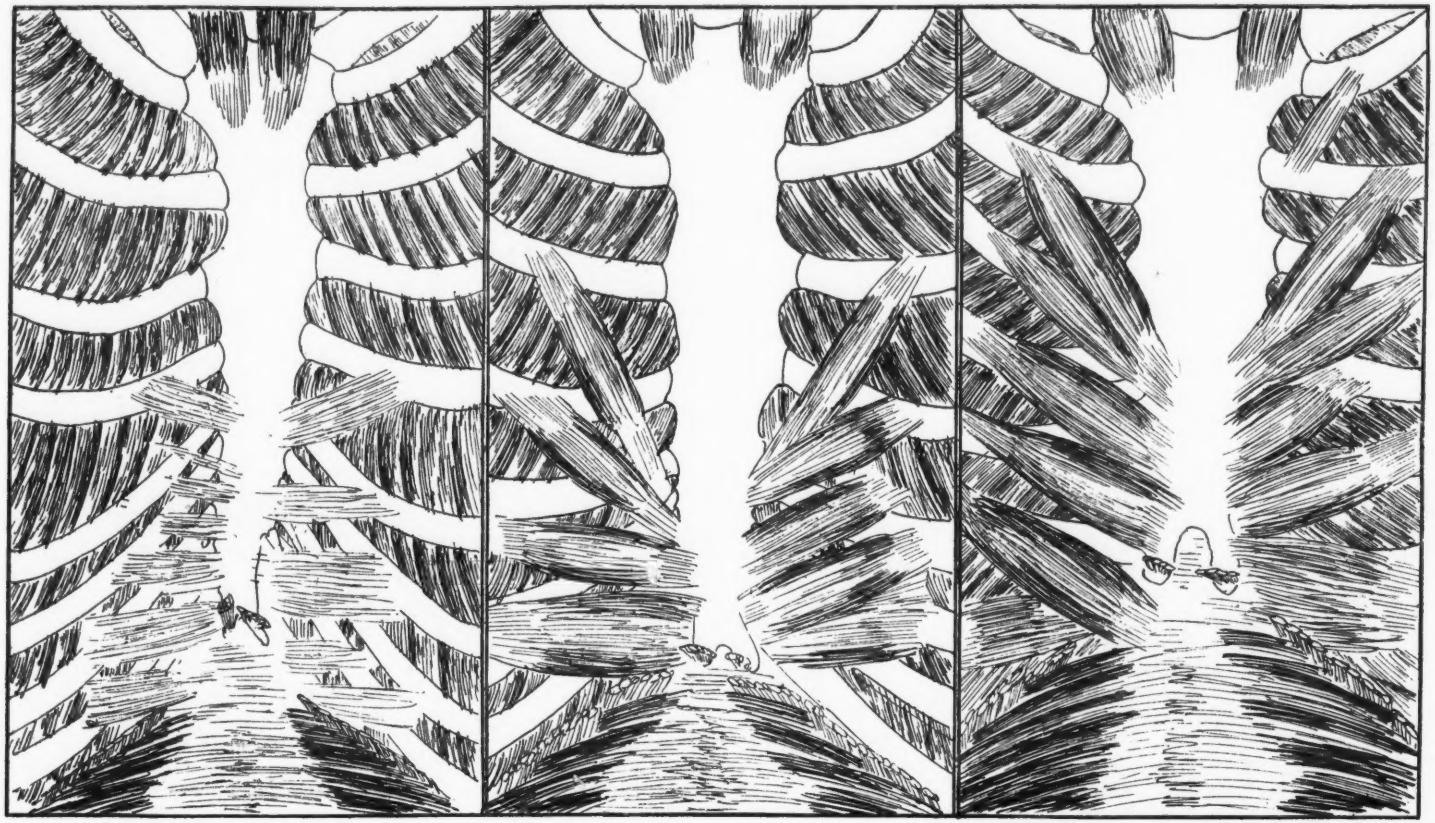


FIG. 10. Posterior aspect of the sternum and adjacent costal cartilages in the three types.
On the right—A type. Centre—B type. On the left—C type.
To show (1) the development of the triangularis sterni; (2) the shape and development of the sternum; (3) the direction of the costal cartilages.
Drawn by Miss Freeman from post-mortem specimens at King's College Hospital.

the individual is erect, but increased when he is supine. The costal portion, on the other hand, is more active in the upright than in the supine posture, and in the crural type acts more as a regulator of the quantity of air, as in phonation, &c., over and above the essential amount which is required by the body: but in the parietal type of chest the costal action will continue when supine. The crural type is the natural, primitive, and automatic form of breathing, as is seen in the breathing of psychic conditions, such as surprise, fear, pleasurable emotion, excitement, and also in asthma, yawning, &c., and in the last gasps which precede dissolution. The crural type is also frequently in evidence in war neurosis, shell shock, D.A.H., &c., where in a large proportion of cases the power of contracting the costal portion of the diaphragm appears to be in abeyance. A similar condition is found after pleurisy and several other conditions, and appears also to lead to general ill health, which disappears on the restoration of the normal movement.

Clinically there are several other points bearing on this question. In the ordinary case of pleurisy the individual lies either on his back or on the affected side, or (if unable to get relief from pain) holds that side rigid by means of the lateral abdominal muscles. In such cases frictions are very audible and are obviously produced in the neighbourhood of the chest-wall. There is, however, another and rarer form of pleurisy, in which at the onset no frictions are audible. The patient cannot get comfortable in any posture. The posture which affords him most relief is the upright, either leaning a little forward, sitting erect, or leaning a little backward. These cases are associated with a pain in the corresponding shoulder-joint, which is therefore not moved, and cutaneous hyperaesthesia to touch and light pinches can be demonstrated in the skin over the shoulder-joint and in areas running up towards the neck, or anteriorly over the upper intercostal spaces. One of my old teachers, Dr. Curnow, who was also an anatomist, explained the condition without any hesitation on the grounds that it was an inflammatory infection of the crus of the same side. I have not been able to find any writing of his bearing on this point. On the suggestion of Professor Barclay Smith, Mr. Alwyn Compton, in the anatomy department of King's College, dissected a foetus and found a clear connexion between the phrenic nerve and the posterior root ganglion of the fourth cervical nerve. This anatomical finding adds strong support to the clinical explanation of the condition.

These two types of pleurisy show marked differences. In the first, relief is obtained by assuming the posture in which the costal portion of the diaphragm is in abeyance. The second and rarer form cannot get relief, but assumes a posture in which the costal portion of the diaphragm is thrown into activity. The fact of these cases being unable to get relief in any position must be attributed to one of two conditions: either the decussation of the crus prevents rest, in that the pull of the unaffected side makes itself felt on the affected side in inspiration (even if the fibres of the affected side should be in abeyance), or the crura are so important to the act of breathing that their activity cannot be

Drawn by Miss Freeman from post-mortem specimens at King's College Hospital.

dispensed with. The latter suggestion is supported by an experimental fact that the rabbit dies directly the crura are detached from their origin from the spinal column.

It will be recalled that of the original series of uncomplicated operation cases, thirty in number, eleven only showed signs of deflation of the lower lobes. These cases were examined irrespective of the time which had elapsed since the operation. In a subsequent series examined within seventy-two hours of the operation deflation was present in practically every case, the exceptions being those cases which recovered rapidly and were able to move freely in bed. A deflated lobe expands rapidly, and after ten or twelve deep and complete breaths few abnormal signs can be detected. Although deflation occurs more rapidly and completely in the crural type of breathing, definite evidence will be found in the parietal type. In the post-mortem observations the lower lobes of one subject, of an obviously parietal type, were found bound down behind a transverse diameter passing through the points where the phrenic nerves enter the diaphragm. This is a clear indication of the occurrence of the condition during life. Clinically the crural type deflate from the extreme base, but the parietal from a point nearer the apex. This is the more remarkable when it is remembered that every individual, not excluding the parietal type, tends towards crural breathing when supine for even a few hours.

When the supine posture is adopted for any considerable period, as in the case of fractures, spinal lesions, &c., the crural type frequently gives place to the parietal type. This change is not heralded by any crisis such as a ' collapse attack ', but seems to be dependent on abdominal distension. A case of typhoid fever recently under my care supplies a good instance of this condition. In the acute stage of the fever, in a relapse extending over a period of ten days, and for a fortnight afterwards, the respiration was of the parietal type. During this period the abdomen was distended. With the passing of the distension the crural type appeared, alternated with the parietal type for a few days, and finally became permanent.

The faculty of distending the abdomen by the contraction of the costal fibres of the diaphragm may remain in abeyance for long periods extending to months. This is not uncommon after pleurisy, when it may naturally be attributed to inflammation of the muscle or pleura, and adhesions. Restoration of function may be expected to be delayed. The same loss of activity may also be found in convalescence after operations, in conditions of mental shock, as in war neurosis, and in sundry other circumstances. So long as this obtains, there will be ill health, categorized as asthenia, &c., and marked improvement in the general health will follow any therapy which restores the normal activity of the muscle, such as training in breathing, restriction of the expansion of the chest laterally, singing, physical exercises, &c. In extreme instances the Japanese method of paracentesis thoracis will frequently be effective.

To any one studying the mechanism of respiration it will be apparent that on taking a moderately deep breath the crural and parietal types appear to achieve

a maximum in one continuous effort, whereas in the B or intermediate type two stages occur. Either the crural type precedes the onset of the parietal type of effort, or the crural type is superadded when the parietal type of effort has reached its maximum. It is possible by education to develop the type of breathing in either form and change from one to the other when desired (Fig. 11).

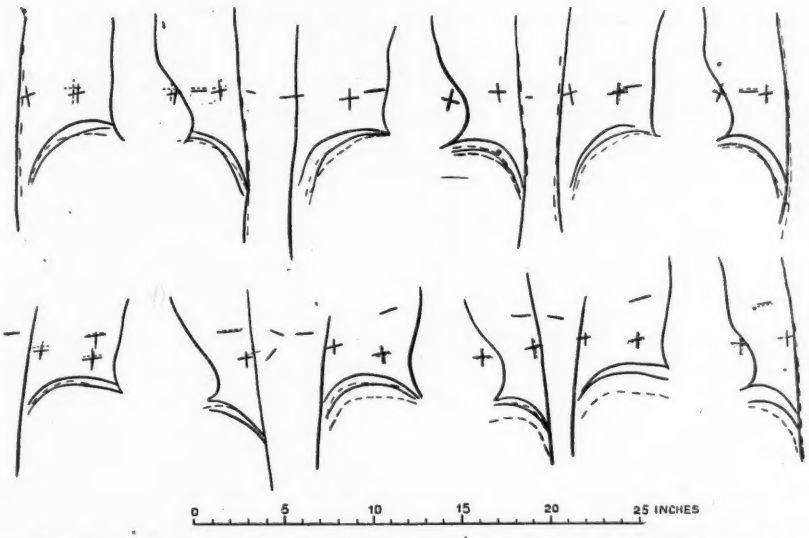


FIG. 11. X-ray tracing from B or intermediate type who has acquired the power of breathing separately both as in the A and C types, but not perfectly in either.

Upper row standing. Lower row lying.
Left diagram, top row, A type and deep breath. Standing.
Right diagram, top row, C type and deep breath. Standing.
Central diagram, top row, A type changing to the C type. Standing.
Left diagram, lower row, A type and deep breath. Lying.
Right diagram, lower row, C type and deep breath. Lying.
Central diagram, lower row, A type changing to C type. Lying.

In the A type the deep breath produces a lowering of the diaphragm near the pericardium; in the C type the depression is general.

When changing from the A to the C type the general outline of the diaphragm is lowered.

A maximum deep breath necessitates the action of both A and C mechanisms. It is therefore not recorded.

These several points, embryological, anatomical, clinical, &c., suggest that the diaphragm should not be regarded as a single muscle, and lend support to the view I am advancing.

In the *London Hospital Gazette*, October 1903, Professor Keith propounded the view that the upper lobes of the lungs are expanded directly by the crus through the pericardial ligament. My observations support this contention, but I consider there is evidence that the action of the crus is in two directions: through the pericardial ligament on the root of the lung expanding the part of the lung above this level—especially when erect—and on the base of the sternum

through the trefoil tendon and the 7th and adjacent ribs bending the sternum, and so expanding the thoracic cavity which lies above the 2nd rib, especially when supine. In either case the action would appear to be on that part of the upper lobe lying above the 6th rib. The costal portion of the diaphragm seems clearly to expand the lower lobe. The middle section of the lung—the middle lobe on the right side and the corresponding part on the left—is, I believe, expanded so far as the diaphragm is concerned, by either the crus or the costal portion. In one type of chest the crural action is developed at the expense of the costal, and vice versa.

It has been pointed out that in crural breathing, when the individual is standing, no antagonist muscle may be detected, but when he is lying supine—and the same is true when reclining at an angle of about 35°—the scaleni may contract in expiration and the triangularis sterni generally does so. Most individuals tend to the crural type of breathing when supine or when the back is comfortably supported by pillows. The abdomen therefore, as a rule, will be found to be flaccid, and the triangularis sterni will be the only muscle active in expiration; but in parietal breathing the scaleni, triangularis sterni, transversalis abdominis, and in varying degree the lateral abdominal muscles, come into action in inspiration, and the latter act also in expiration. The synergists to the crus are to be found in the paraspinal muscles in the thoracic region. I have not been able to find any writing which bears on the action of synergist and antagonist muscles in the presence of inflammatory affections of the principal muscle. The synergists might be expected to act in some proportion to the degree of contraction of the principal muscle and the antagonists simply as restorers of the original state or in the direction of preventing pain.

The Effect of Dyspnoea.

In dyspnoea progressing in degree, changes occur in the ordinary crural type which, when the difficulty is marked, culminate in the addition of the parietal type. The accessory muscles show corresponding changes.

Table A illustrates this point.

It will be seen from the table that the triangularis sterni and transversalis abdomini, which under normal conditions are inoperative, in dyspnoea are called into action to an excessive degree, first as antagonists to the crus, later as synergists to the costal part of the diaphragm.

Overaction may lead to pain on pressure, as shown in Table B. The patient was an elderly man who had had pleurisy some ten days earlier, and in whom friction sounds were present over a limited area between the nipple and mid-axillary lines on the left side. There was no pleuritic pain on the day of examination. His chief complaint was that of waking at night, after two or three hours' sleep, with pain behind the sternum and along the free margin of the ribs anteriorly on the left side. Pressure on the triangularis sterni and transver-

salis abdominis on the left side produced pain which was recognized as the pain in question.

On lying down part of the parietal mechanism went out of action, as is generally the case. This is shown by the change in the triangularis sterni. The pain experienced on waking in the night was due to the fact that in the supine posture the lateral abdominal muscle was out of action as a result of the pleurisy, and the two remaining muscles of expiration on that side were called upon to do extra work and therefore became tender and painful on

TABLE A.

Crural Breathing (Supine), Accessory Muscles, &c.

	Normal.	Stages of Dyspnoea.		
		(1)	(2)	(3)
Subclavicular region expansion	Little	Increase	Diminished	
Eversion, middle and lower ribs	Little	Increase	Increase	
Lower sternal recession	Slight	Increase	Very marked	Less marked
Epigastric movement	Slight recession	Recession	Marked: inversely proportionate to degree of contraction of transversalis abdominis	Wavy movement, no recession or procession. Transversalis abdominis contracting prevents recession which, however, may occur below the umbilicus
Scaleni	Nil	Expiratory	Inspiratory and expiratory	Inspiratory
Triangularis sterni	Nil	Expiratory	Inspiratory and expiratory	Tonic
Transversalis abdominis	Nil	Nil	Expiratory. A, B, and C act according to the degree of dyspnoea. (A between 8th costal cartilages, B between 9th, C lowest ribs to umbilicus)	Tonic
Lateral abdominal muscles	Nil	Nil	Expiratory	Expiratory strong

Stages (2) and (3), parietal type in addition to crural.

pressure. Pain on pressure is not at all uncommon in these muscles. I have lately seen several patients with symptoms of angina pectoris, in whom the area of subjective pain was characteristic. These identified the pain produced by pressure on the triangularis sterni on the left side as *the* pain, though it did not induce the subjective pain in the left arm which accompanied the attack.

Recently I saw typical examples of this tenderness in two patients in the surgical ward. Each complained of epigastric pain in the early morning on the second night after operation; their respirations rose to 40–45 per minute and the pulse-rate to 150. The temperature did not rise above the normal and the distress lasted for five or six hours. Each of these patients complained of tenderness when the triangularis sterni was palpated, and each had changed from

the crural to the parietal type of respiration at some time during the night. The triangularis sterni muscle, instead of being operative during expiration only, was at first tonically contracted during both expiration and inspiration, and subsequently became inspiratory in action for a period of from 24 to 48 hours, and then became expiratory as the crural type of breathing was again resumed. The sister of the ward stated that such pain was quite common, and was usually explained by the patient as being due to wind. It passed off with the action of the bowels (generally about 48 hours after the operation) following a dose of castor oil. I suggest that this tenderness is due to the muscle becoming fatigued. It has to undertake control of the chest both in inspiration and expiration, owing to the distension of the abdomen producing the parietal type of breathing, in addition to its expiratory action natural to the supine posture and crural breathing. When the abdominal distension is relieved the muscle resumes its action as an expiratory muscle only, and has time to rest during inspiration, the parietal type of breathing having given way to the crural type.

TABLE B.

Crural Type of Breathing.

Case. Pain in retrosternal region and in the left costal margin anteriorly, with dyspnoea on walking, and after sleeping for three hours.

	Standing.	Lying.
Chest	Moves slightly	Infraclavicular, procession no rise of sternum
Eversion of ribs	Nil	
Epigastric movement	Little, abdomen distends generally	Rises to level of rib margin with inspiration, falls with expiration. No procession of abdomen
Lower sternal region	Slight recession	Recession increased
Scaleni	Inspiratory	Not acting
Triangularis sterni	Expiratory and inspiratory	Expiratory
Transversalis abdominis	Expiratory	Expiratory
Lateral abdominal muscles	Expiratory	Rt. expiratory, *Lt. nil*

I have also noted tenderness of this muscle in other cases in which pleuritic frictions were present, the lower lobe of the lung being involved. In each case similar symptoms had occurred, namely, tachycardia, rapid breathing, general distress, and rise of temperature. The onset was sudden and the duration less than twenty-four hours. A similar explanation may be given of the pain felt along the margin of the ribs extending towards the axilla. It is almost accurately limited to the origin of the costal portion of the transversalis abdominis and is to be attributed to an unnatural tension of this part of the muscle, such as would arise were either a combination of prolonged crural and parietal breathing necessitated, or costal fixation, to prevent movement on that side. Possibly, however, this pain may also be due to direct inflammatory invasion of the muscle itself. It should be remembered that the lymphatics from the abdomen pass upwards by two chief paths, the one through the aortic

opening of the diaphragm, and the other through the space left between those parts of the diaphragm which arise from the sternum and from the adjacent cartilages. The triangularis sterni and transversalis abdominis are thus very liable to be involved in any extension of the inflammation along the lymphatics.

The Respiratory Conditions in Pleurisy.

The following muscle reactions occurred in a man aged 54 on the third day of the illness, in whom frictions were audible between the left nipple and the mid-axillary lines:

TABLE C.

		Standing.	Lying.
Upward movement of chest		Slight	Nil
Eversion of ribs		Raised and drawn in	Raised
Lower sternal recession		Slight	More marked
Epigastrium		No movement, some procession below umbilicus	No movement, procession below umbilicus diminished
Scaleni		Nil	Inspiratory, Rt. > Lt.
Triangularis sterni		Expiratory Rt. > Lt.	Expiratory Rt. = Lt.
Transversalis abdominis			
vide Table A	A.	Tonic, increased with expiration	Inspiratory Rt. < Lt.
	B.	Tonic, increased with expiration	Inspiratory Rt. Tonic Lt.
	C.	Rt. Tonic, increased with expiration	Inspiratory Rt.
		Lt. No tone, contracts in expiration	Nil Lt.
Lateral abdominal muscles		Expiratory	Nil Rt. Tonic Lt.

This was a more severe case than the preceding; pain was experienced with an inspiration deeper than the minimal. The crural antagonist acted naturally but was somewhat less active on the side affected.

The synergist on the side of pleurisy was on the whole *less* active than on the normal side. The transversalis abdominis and lateral muscle on the side of the pleurisy were more active than those on the right and kept the side of the chest fixed. The former was tender to pressure. It may have been actually inflamed, or hypersensitiveness may have been referred from the costal portion of the diaphragm. It does not seem possible to ascribe the tenderness to over-exertion in this case.

The costal antagonist on the affected side was not more active than on the normal side when standing, but was over-acting when lying. A tonic condition of the lateral muscle of the affected side is the rule in the ordinary form of pleurisy during the first few days, and is, indeed, the first sign of the condition. When Captain Gompertz was resident at the Evelina Hospital in 1907 we were able to prophesy on which side a basal pneumonia was going to develop, by the comparative diminution of the measurement of the side of the chest, consequent upon this contracted condition of the lateral muscle. This diminution takes place some hours before any other localizing sign can be

detected. Later the lateral muscle becomes flaccid, as has been shown above. It would seem likely that this is indicative of a corresponding change in the condition of the diaphragm, to the costal portion of which it is synergist and antagonist.

The muscular reactions in the other and rarer form of pleurisy are given in the next table. The man was too ill to stand up, but was reclining at an angle of about 40°.

TABLE D.

W. Male, 60. Fourth day of illness, very big chest, obviously crural type: at the onset, agonizing pain in chest and behind the sternum, commencing suddenly, pain in left shoulder, and pain on swallowing.

Chest movement	Only lateral expansion, left apex flattened and little procession
Eversion of ribs	Present but already everted
Epigastric movement	Recession
Lower sternal recession	Marked
Scaleni	Expiratory Rt. and Lt.
Triangularis sterni	Rt. expiratory with slight tone. Lt. nil. Lt. epigastrium quite flaccid. Lt. margin of ribs tender from mid-axilla to mid-line
Transversalis abdominis	Rt. expiratory with slight tone. Lt. nil
Lateral abdominal muscles	Expiratory Rt. > Lt.
Apex beat	5th space, nipple-line uncovered
Liver dullness	6th rib
Apices	Rt. breath-sounds good. Lt. breath-sounds deficient, puerile, or bronchial
Lower lobes	Rt. breath-sounds good. Lt. post-axillary area to spine faint, tubular breathing, and aegophony. Resonance diminished. Friction-sounds were audible over the chest-wall near the lower border, between the anterior and mid-axillary lines
Pulse	92
Respiration	28
Temperature	101·4°, subsequently falling to normal

Diagnosis: Left-sided diaphragmatic pleurisy with deflation of the lower lobe and partial deflation of the upper.

In this case the lower lobe on the left side was fairly completely deflated and the upper lobe partially so, as judged by the physical signs. No sputum was expectorated, and from the physical signs it was not to be anticipated. The presence of pain on swallowing strongly suggested an affection of the crus of the diaphragm, as did the shoulder pain, for which an explanation has already been given. The type of breathing was generally crural, though the costal portion on the right side was acting, as evidenced by the good air entry at the base, and by the triangularis sterni and transversalis abdominis on the right side exhibiting some tone during the whole phase of respiration, in contradistinction to those on the left side where the muscles were quite flaccid. The lateral abdominal muscles contracted weakly. The flattening of the left apex and defective air entry, the uncovering of the heart, with apparent displacement, indicated deficient expansion of the upper lobe and suggested a deficient action of the left crus. The antagonists to this portion of the diaphragm were out of action. The signs and muscle reactions also suggested defect of the costal portion of the muscle.

Contrasting the muscle changes in the last two cases when at rest, it is seen that in the costal type of pleurisy the crural antagonist is acting naturally but

less strongly than its fellow, the costal is overacting. In the crural type the costal antagonist is weak, the crural is in abeyance. In the parietal type the synergists to the costal portion of the diaphragm are acting irregularly, but as a whole more strongly than their fellows of the unaffected side. In the crural type the costal synergists are out of action. Unfortunately no record was made in either case of the crural synergist. In other cases the paraspinal muscles have shown variations.

However, the differences exhibited by the antagonists is sufficient to suggest that the affection in these two cases is very different. The dissimilarity of these actions suggest that the antagonists serve the organism best by preventing pain, rather than by acting in a uniform manner. In costal pleurisy it is known that the diaphragm is high in the chest and practically immobile. It may be in a lax condition or in a state of passive contraction, not allowing of any movement. The synergist action would suggest the latter, for it might be expected to conform to the action of the principal muscle more clearly than the antagonist. The intense retrosternal pain in the crural type at the onset would suggest that the muscles situated there (the crural antagonists) had been in a state of over-activity and finally gave way.

The case quoted above illustrating the second type of pleurisy presented all the characteristic signs of post-operative massive collapse in a mild degree, but there was no acutely sudden and severe onset.

There was: (1) the falling in of the apex; (2) the deflation of the lower lobe; (3) cardiac displacement; (4) characteristic pain; and (5) flaccidity of the abdominal wall on the affected side.

In respect of these various signs I would put forward the following explanations:

(1) The falling in of the affected apex is due to lack of distension of the underlying lung by the defective action of the crus of the diaphragm of the same side. Probably neither upper lobe can be completely deflated, because of the action of the crus on the opposite side. Either crus acting through the pericardial ligament must have a certain effect on the root of both lungs, though such effect will be less on the contralateral side.

(2) Deflation of the lower lobe results from loss of action of the costal portion of the diaphragm on the affected side.

(3) Cardiac displacement in the case recorded above was not as great as in the early stages of 'post-operative massive collapse'. A differentiation has to be made between the actual displacement on the one hand, and the uncovering of the heart by a retracted lung, with or without dilation of one of the cardiac chambers, on the other. It is well recognized that when lying on the left side the apex beat may, after a short time, be palpable against the ribs in the axilla. This may be explained as resulting from the retraction of the lung, situated between the heart and the chest-wall. Normally, in the crural type when supine there is apparent displacement of the apex beat upward and to the left. X-ray examination shows that this condition coincides with the elevation of the

diaphragm, and is really a rotation of the apex round a point situated somewhere in the base. *Post mortem*, when the lungs are expanded, it is not easy to displace the mediastinum to either side. No opportunity has occurred to make such an observation when the lower lobes are markedly deflated. On the other hand, in a patient recently in hospital with empyema of the left side and caseous bronchopneumonia of the opposite lung, the heart was seen pulsating as far out as the right nipple. No pulsation could be detected on the left side of the sternum. An X-ray photo showed the position of the heart on the left side to be nearly normal, and a polygraph tracing indicated that the pulsation on the right side was auricular in time. *Post mortem*, the middle lobe of the right lung was deflated in half its extent and solid in the other half. There was, therefore, a withdrawal of the lung covering the right auricle. In this case dilatation of the right auricle with retraction of the right middle lobe would satisfactorily explain the pulsation found to the right of the sternum, without invoking a considerable degree of mediastinal displacement. That there is grave disturbance of the circulation is shown by the rapidity and irregularity of the pulse, during and after the collapse attack. An appreciation of the physical signs consequent on deflation of portions of the lung leads me to place less importance on 'cardiac displacement' than is attributed to it by Pasteur.

(4) The origin of pain in the retrosternal region has been discussed earlier in the communication. It is one of the constant phenomena of the collapse attack and may commence some time before the acute symptoms, or may coincide with them. Pasteur does not lay great stress on the pain in swallowing or pain over the shoulder. In the cases I have seen the former has been present, especially when the left side was affected, and the latter in the most severe cases.

(5) Flaccidity of the abdominal wall in the epigastrium on the affected side has also been discussed. The conclusion reached was that flaccidity, occurring in the triangularis sterni, transversalis abdominis, and lateral muscle, suggested that both the crus and costal portions of the diaphragm on this side were affected and probably out of action. Some inspiratory eversion of the lower ribs on the affected side must result from the action of the crus on the unaffected side. This affords a reason for the action of the lateral muscle on the affected side, and also for the weaker contraction. Space does not permit of any discussion as to the effect of interaction of the crus and costal portion of the diaphragm.

The suddenness of the onset of acute symptoms in the collapse attack is difficult to explain. The condition immediately preceding the attack, and resulting from the supine posture, is: both lower lobes are deflated, the parietal breathing mechanism is in abeyance, and respiration is being carried out by the crura expanding the upper lobes. The findings in the attack indicate that the upper lobe of the unaffected side is hyperactive, the lower lobe of this side is in the normal condition, while on the affected side the upper lobe is partially, and the lower lobe completely, deflated. At the onset of the attack, therefore, the lower lobe on the unaffected side has to be brought into action, while the upper lobe on the affected side becomes partially out of action. I have already cited

cases where the change from crural to parietal breathing, without any apparent accessory event, caused a considerable general disturbance, especially in the rate of the heart-beat and of respiration. This induction of the parietal mechanism to expand the lower lobe on the unaffected side might be suggested as a sufficient explanation of the sudden onset of symptoms. I stated that in the marked cases of the crural type of breathing I was physically unable to change their normal type into that of the parietal type of breathing, and in them a considerable disturbance under these conditions might well be expected. I also mentioned that in the high paraplegia distress followed the attempt to convert the type of breathing by thoracic pressure. It is worthy of note that Pasteur lays great stress on the physical development of his cases. Such expressions as 'magnificent physique', 'well-developed chest', 'Rugby football player', occur with some frequency in his protocols. It is precisely to those individuals of the most characteristic crural type of breathing that such a description applies.

There is, however, another explanation which should be considered. Assuming that one of the crura which are expanding the upper lobes first becomes inflamed and then suddenly ceases its action, there would be a sudden loss of more or less than half the expanding power (according to which crus is affected). The result of this would be to cut off suddenly a considerable area for aeration. Lichtheim (17) showed that the introduction of a laminaria tent into the bronchus of one lobe of the lung of a dog produced a very severe condition, the predominant signs indicating sudden dyspnoea and heart failure. Symptoms of similar severity were not observed when pneumothorax was produced or when the bronchus was ligatured through the chest-wall, the latter procedure involving a degree of pneumothorax. The condition, therefore, followed on obstruction to the bronchus with sudden loss of considerable aerating surface, but without similar interference to the circulation, as would occur with pneumothorax. This would seem to parallel closely the condition at the onset of the post-operative massive collapse attack, where, as the result of spasm and default of one crus, a large aerating surface is rendered inoperative without any corresponding circulatory restriction. The attempt of the antagonists to limit the movement of the chest-wall would lead to exhaustion, pain, and ultimately to defeat. Possibly this latter explanation is more in accordance with the very sudden type of case, and the former with that condition which develops insidiously.

Pasteur discusses the possibility of pleurisy being a factor in the production of the collapse attack only to discard it, and yet in a considerable proportion of his cases, at one time or another, the presence of friction-sounds is recorded. Further, in the cases in which a 'collapse attack' was noted in non-operative conditions, pleurisy was most likely present, e.g. in pneumonia, pyaemia, &c. In the cases I have seen, friction-sounds have been detected in roughly 33 per cent. of cases. A very small patch of friction will produce changes in the synergists and antagonists such as I have recorded, and on several occasions when these muscular actions were abnormal I have found small areas of friction

which had escaped detection. I am gradually coming to the opinion that those reactions definitely indicate the presence of a lesion in the several areas of the pleura, and where associated with pyrexia—as occurred in all these post-operative cases recorded by Pasteur and in those seen by myself—I feel justified in assuming the presence of a lesion of an inflammatory nature. In Pasteur's cases a septic focus was present in each instance, though he minimizes the degree of sepsis. In a post-mortem performed recently in a case of scirrhus of the oesophagus near the cardiac orifice, in which there was extensive diaphragmatic pleurisy, a small focus of infection was found in the form of one stitch abscess, the size of a threepenny-piece, in the wall of a gastrostomy wound. This is a smaller area of infection than is discarded as non-effective by Pasteur in some of his cases.

It is, however, not necessary to prove the presence of a (surgical) septic focus from which the infection could travel to the diaphragm through the anterior or posterior lymphatic channels and reach that muscle in the region lateral to the sternum or between the crura. The infection may come through the lung, the lymphatics of which largely travel towards the pleura. In fact, in a lung freeing itself from infection, a large amount of débris will be found near the pleura at the points where the fibrous trabeculae join the sub-pleural connective-tissue layer. From such, infection easily reaches the pleura, and is a frequent method of infection of this membrane. Small areas of consolidation with pleurisy may oftentimes be found in the free margins of the lobes. Dissemination over the pleura is easily produced.

Conclusion.

The symptoms and signs of the syndrome known as diaphragmatic paralysis are, therefore, to be attributed to an exaggeration of the normal phenomena of breathing when supine, such exaggeration being due to prolonged maintenance of that posture, owing to general weakness and toxaemia. The normal inspiratory action of the diaphragm in the supine posture is carried out by the contraction of the crura, the costal portion being in abeyance. The inactivity of the costal portion is greater according to the approach of the individual to the type of breathing designated as crural, and the tone of this part of the muscle will be diminished in accordance with the degree of toxaemia and the weakness of the individual. The phenomena of the 'post-operative massive collapse attack' are produced by the onset of inflammation, affecting the pleura covering the diaphragm—especially that part in the region of the crura—or affecting the muscle of the crus situated behind the peritoneum, in an individual in whom the lower lobes are already deflated.

It will thus be seen that there is not such a great difference between the theory put forward by Pasteur and the present one. Whereas he attributes the condition of the lungs found in diphtheria to paralysis of the diaphragm, I consider that it is the result of a natural condition in which the costal portion

of the diaphragm is in abeyance, the crural portion alone contracting. This type of breathing occurs in individuals who have a particular form of chest.

The post-operative collapse attack is regarded by Pasteur as due to a reflex arrest of one half of the diaphragm. My contention is that one half of the diaphragm and its synergic and antagonistic muscles are out of action owing to inflammation of the muscle or of the pleural membrane covering it, and generally where Pasteur invokes inspiration as most important I am led to emphasize the importance of posture and alterations in the action of muscles accessory to the diaphragm.

Taking a broad view of the pulmonary conditions which give rise to anxiety after operations, I believe with Pasteur that the majority are dependent upon, or influenced by, deflation, which, as I have shown, is a normal consequence of prolonged supine posture. If they are divided into those without pain and those accompanied by pain (excluding the pain of the incision), I think it will be found that the latter class only are associated with pleurisy. A very small patch of pleurisy may produce great pain and at the same time be quite difficult to detect. Such small areas of pleurisy are by no means unusual. In patients not actually ill, where the muscular actions were abnormal, I have found several instances where friction-sounds were only audible over an area of about the size of half a crown, and unless particularly careful search were made for them would be overlooked, as had indeed been the case. I am led to believe that such pain should always be attributed to pleurisy when pyrexia (for which no other cause can be found) is present. A solitary exception with regard to pain that I would make occurs in the type of cases of which I have quoted two instances in which no pyrexia occurred, the pain resulting from fatigue of an individual muscle, or muscle group; but even here the possibility of pleurisy, insufficient to produce pyrexia, cannot be excluded.

Of those cases which cause anxiety and are not associated with pain, the majority seem to be due to the presence of secretion in the larger tubes, of varying nature, always infective but not always purulent. These cases are characterized by a frequent unproductive cough similar to that which is usually associated with empyema. Such a patient will cough in a half-hearted way in the middle of every sentence, and perhaps only expectorate two or three times in the course of the day. The explanation is that the lower lobes are deflated, there is thus no opportunity for a volume of air to accumulate behind the mucus. In the majority of cases nothing further happens, and as strength is recovered and the patient resumes an alternative position inducing parietal breathing, the lobe expands, and material is expectorated with cessation of the irritation. It is, however, far from uncommon to find that when the expectorated material is purulent the inflammation affects the smaller tubes and bronchiolitis results. The spread may be due to aspiration of the infected material, or by direct extension with progressive descending inflammation of the smaller tubes, and may terminate in broncho-pneumonia. It is but a short step from this condition to the development of pleurisy with the associated pain and the development of

the acute 'collapse attack'. It would, however, seem most probable that the condition described above, viz. infection through the bronchial tubes, while accounting for the majority of the less severe attacks, does not explain the most acute and alarming conditions, which more likely originate from affection of the crus below the level of the diaphragm. While attacks of lesser intensity are common, those of the greatest severity are relatively rare, and have not usually been associated with preliminary signs.

Finally it must be recognized that the supine posture is quite as abnormal as is the condition of prolonged repose. Hence, as far as possible, these two factors should be eliminated from medical and surgical practice. The general trend, especially among surgeons, seems to be in that direction.

The clinical and post-mortem work was carried out at King's College Hospital, St. John and Elizabeth Hospital, and the Evelina Hospital.

The experimental work was performed at King's College, in a private laboratory, and in the physiological and pharmacological laboratories.

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DESCRIPTION OF PLATES.

PLATE 8, FIG. 2. Specimen obtained from a patient dying with a lesion at the eighth cervical segment.

The external or lateral surface of the right lung is seen showing the various fissures, and posterior to the right lung a small portion of the left lung. The lower lobe is small and completely deflated.

FIG. 6. Photograph of the lungs removed from a patient dying from the result of pulmonary embolus 72 hours after an abdominal operation.

The interlobar fissure is well seen on the left side, below which a small area of the lower lobe is not deflated.

On the right side the fissure is almost completely obliterated. At one point an attempt has been made to open it up. The lower lobe in the immediate neighbourhood of the fissure is not deflated. Except for these two areas the lower lobes are completely deflated.

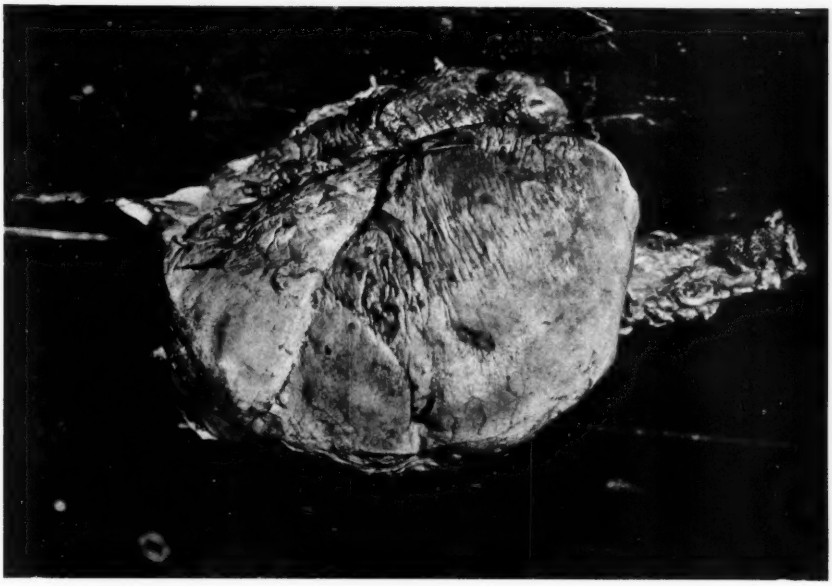

FIG. 2

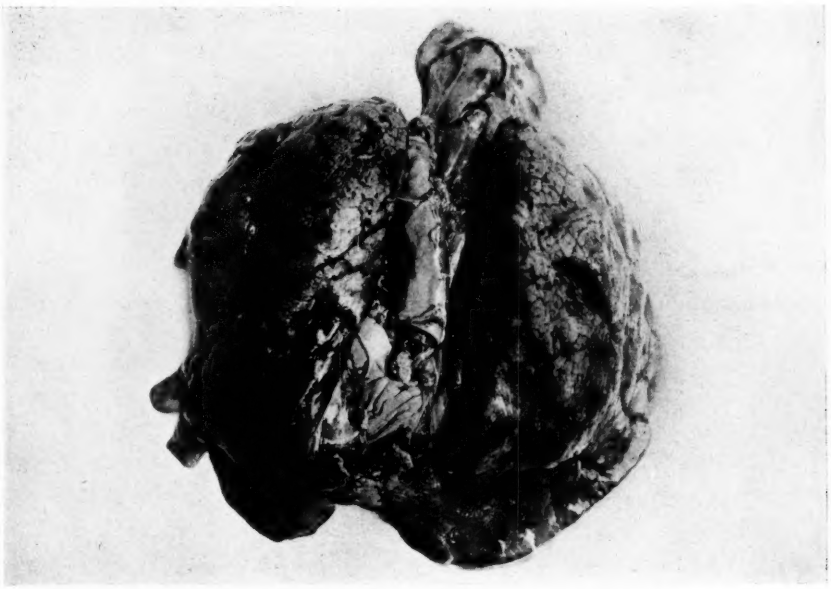

FIG. 6

BERI-BERI IN THE MESOPOTAMIAN FORCE

By C. A. SPRAWSON

The occurrence of a number of cases clinically resembling beri-beri in the Mesopotamian Force from 1915 to 1919 gave rise at the time to much investigation and discussion.

Entire agreement was not always reached as to whether the diagnosis of beri-beri was correct. It was admitted by all observers that there was no clinical difference between the text-book description of the disease and the cases seen in the field; but because in some instances no defect could be found in the diet some observers considered the disease could not be beri-beri. Others classed the disease as beri-beri, and considered it likely that some other cause than food deficiency was here operative. It will be understood, therefore, why an unknown number of cases amongst British troops was in the earlier days returned as 'peripheral neuritis', while exactly similar cases were later classed as 'beri-beri'. The total number of beri-beri cases is therefore somewhat larger than that here reported. Now that the campaign has come to an end there is opportunity to review the facts and to consider what the correct view of these cases should be. It may be stated here that the frequently simultaneous occurrence of signs of nerve degeneration in the lower limbs and of cardiac signs, which we may call 'cardio-neurotoxic syndrome', is the chief characteristic of the disease. The terms 'cardio-neurotoxic syndrome' and 'beri-beri' will be used indiscriminately; that is to say, the latter word will not necessarily imply that a vitamine deficiency was the cause of the condition.

The cases returned as beri-beri during this campaign may be classed into three divisions: (A) British cases, occurring amongst the land forces. Of these there were 84 in 1917 and 51 in 1918. But, as already explained, some other cases were returned as 'peripheral neuritis'. (B) Chinese cases, amongst Chinese labourers on land. Of these there were 647 in 1917, 198 in 1918, and 76 up to the end of September, 1919. (C) Ship cases, occurring amongst Indian crews. There was a small epidemic in 1916 and another in 1918. There were practically no Indian cases on land.

It is the opinion of the writer that though the clinical picture is approximately the same in each of the three classes of cases, and though the pathological lesion is also in all probability approximately the same, yet that the etiology of each class is different. In the etiology of this cardio-neurotoxic syndrome there

appear to be two main predisposing causes, food deficiency and infection. The exciting cause may be fatigue, secondary infection, or other depressing factor. If this be correct, the syndrome may arise under entirely different circumstances, and the measures necessary for its prevention or treatment should accordingly be varied to suit the particular instance. Concerning these classes, the writer's views are:

(i) That the British cases were not due to a food deficiency; but that they were of infective origin.

(ii) That the Chinese cases have previously suffered from beri-beri in their own country, the result either of diet deficiency or infection; or else they have lived for a prolonged period in such a state of vitamine deficiency that illness, or fatigue, or other depressing cause may allow the ill effects of this long-standing deficiency to evince themselves.

In other words, that they were suffering from 'latent beri-beri' when they landed in Mesopotamia.

(iii) That the ship cases were examples of the orthodox primary beri-beri, arising from recent vitamine deficiency. This primary beri-beri can be readily prevented by attention to the diet; but once the syndrome has developed cure is sometimes tardy.

This conception of the human cases of beri-beri is still more comprehensible when compared with the results of animal experiments, such as McCarrison's observations on birds. In 1914 (1) McCarrison, by means of infection with Bacillus suipestifer, induced polyneuritis gallinarum in birds fed on abundance of mixed grains.

Birds that survived the bacillary infection for six days developed polyneuritis: these correspond to the British cases (Class A) in which the presence of an infection is suggested. McCarrison's male pigeons (2) that took on an average sixty-one days of totally avitaminic diet to acquire beri-beri correspond to the ship cases (Class C), where, as will be shown, five months of a partially avitaminic diet were sufficient to induce the disease in men.

McCarrison also found that with the combined factors of deficient diet and infection acting together the cardio-neurotoxic syndrome developed in birds with greater readiness than when either factor acted alone. It is suggested that the Chinese of Class B are analogous to these pigeons.

A. *British Cases of Beri-beri.*

It has often been proved that consumption for several weeks of a diet deficient in vitamines will cause in birds degeneration of certain peripheral nerves and, as McCarrison (2) has recently shown, widespread endocrine changes. The work of Eijkmann (3) and others is sufficient evidence that a diet of polished rice may cause beri-beri in men. Reason must be given therefore for holding the opinion that these cases amongst British soldiers, which appeared clinically so like beri-beri, were not due to food deficiency but to some infective cause. Opportunity

was afforded for studying the disease in epidemic form in a certain British regiment in Mesopotamia on two occasions, whilst the records of another British unit show that the disease also was endemic amongst them.

The regiment first referred to was encamped at Shaiba, about eight miles from Busra, in the latter half of 1916. By the end of the year sixty-six cases of so-called beri-beri had occurred, most of them in December. This epidemic was investigated by the Medical Advisory Committee (4) and by Colonels Wilcox and Melville, Consulting Physicians to the Force, and by Major Stevenson of the Base Central Laboratory. Reference will be made later to their reports.

In the beginning of the year 1917 the disease died out, and in April the regiment moved about 100 miles to Nasiriyeh. In December 1917 there was a similar epidemic in the regiment, then at Nasiriyeh: on this occasion there were only fourteen cases and the epidemic was investigated by Colonel Melville and Major Stevenson.

To return to the first or Shaiba epidemic, the Medical Advisory Committee in their report remark that beri-beri had occurred about the same time the previous year in other units. This, together with its recurrence in December 1917, suggests that this syndrome is more prevalent in the autumn.

A clinical account of a typical case of this disease will now be given, a sporadic case being selected because the subject was himself a medical officer and able to give an accurate and detailed account of his symptoms. The Shaiba cases will be referred to later.

Captain 'C.', a medical officer, aged 26, stationed in a camp on the line between Baghdad and Persia, suffered from diarrhoea in the first week of November 1917. For two or three days there was a rise of temperature to about 100° F. On recovery from the diarrhoea the patient noticed weakness of his legs, and for this complaint was admitted to hospital on November 10. At this time were noted tenderness of the calves and exaggeration of the knee-jerks, together with some palpitation on walking and slight swelling of the feet. With this clinical history the patient was evacuated to Baghdad.

The patient stated that his diet in camp, where he was medical officer to an Indian regiment, was particularly good. It appears to have been rich in anti-beri-beri vitamines, for he took porridge daily, dhal occasionally, and eggs often. He ate four fresh eggs daily, exclusive of those in puddings, &c. He ate rice but rarely. No one else in the regiment or in the camp seems to have been similarly attacked.

On arrival in Baghdad the knee-jerks were absent. There was some cardiac dilatation, the apex beat being in the nipple line. There was no tachycardia whilst the patient lay in bed. After five days in Baghdad the patient was evacuated down-stream and reached Amara a week later. On his arrival there the knee-jerks had returned.

On arrival in Busra in the first week of December patches of skin anaesthetic to light touch and to pin-prick were discovered on the tibial aspect of each leg extending nearly half-way from ankle to knee. The apex beat was now noted as

being outside the nipple line. The tenderness of the calves was still present. The patient was evacuated from Busra to India, and after convalescence and a few weeks' leave was fit to return to duty in Mesopotamia. During eighteen months' further duty in Mesopotamia he has shown no recurrence of the disease.

The Shaiba epidemic cases were similar to the above.

Reference need only be made to one in particular because of the patient's short residence in the country.

Pte. P., total residence in Mesopotamia five weeks, all at Shaiba. Onset of symptoms five days before admission, i. e. after one month's residence. This case was severe, the heart being much dilated, with systolic murmurs at the apex and tricuspid areas. There were also muscular weakness and hyperaesthesia of the legs. The knee-jerks were entirely absent.

I am indebted to Captain T. H. Oliver, R.A.M.C., for the report on Pte. P.'s case. Captain Oliver, in a report on fifty-four of the Shaiba cases, notes the following points:

'Dilatation of the heart, usually left-sided, was present in 80 per cent. of cases. Systolic murmurs were common at the apex, pulmonary and tricuspid areas. Tachycardia always resulted from slight exertion. There was some oedema over shins and ankles in about one-third of the cases. Frequently there was a slight evening temperature, especially at the beginning of the patients' stay in hospital. This is apart from the fact that a previous history of malaria was noted in nearly half the cases, a benign tertian parasite found in five cases and a malignant tertian in one case. The knee-jerks were usually normal or increased: they were absent in about one-fourth of the cases. Weakness of the leg muscles was a common early symptom, but sometimes only occurred later. Flabbiness of the calves was common. Anaesthesia was not common in this epidemic: hyperaesthesia was occasionally found. In no case was there any ocular or palatal palsy.'

In most of the sporadic cases which the writer has seen some anaesthesia has been present, occasionally extending up to the mid-thigh and at times of a stocking type. Usually, however, it is in patches and liable to occur about the ankles. Colonels Wilcox and Melville in their report on the Shaiba epidemic say: 'We are satisfied that in the cases examined by us the symptoms were such that the diagnosis of beri-beri was correct.'

The medical officer of the regiment wrote: 'Diarrhoea has been very common in the regiment, and I should say that over 50 per cent. of people coming to Shaiba get diarrhoea, which is presumably due to the water.' But he also remarked that no initial diarrhoea had been noted in the beri-beri cases and some had had no diarrhoea at any period. This is of importance because peripheral neuritis occasionally occurs as a complication of bacillary dysentery or of other enteritic conditions. Regarding the diet of this infected regiment at Shaiba the Medical Advisory Committee wrote as follows: 'Before the attack, troops had a full mixed diet, the only important deficiency being in fresh vegetables, this deficiency of course being equally common among troops at the front and in

many parts of Mesopotamia from which so far little or no beri-beri has been reported.' In December 1916, after 36 cases had occurred, they reported, 'A good and varied diet is said to be given, which includes fresh vegetables. Marmite is also being issued.' Nevertheless, another 20 cases occurred before the end of the year.

The Consulting Physicians, on the other hand, considered that there was evidence of deficiency of anti-beri-beri vitamines in the food as consumed, not so much from deficiency in the rations as from the nature of the Shaiba water, which necessitated prolonged boiling of food articles and therefore caused destruction of the vitamine. They remarked also on the absence of oatmeal and of dhal in the dietary.

There must, however, have been numbers of other troops who had neither oatmeal nor dhal, since the whole British force were on the same rations: yet no other unit developed an epidemic such as this. Moreover the fact that next year the disease recurred in the same British unit in another place and under a satisfactory diet and water-supply also would suggest that the diet at Shaiba was not to blame.

There had previous to the arrival of this regiment been two Indian regiments at Shaiba. They occupied part of the same camp the British did and used the same water-supply: none of these Indians developed beri-beri. It has already been mentioned that there have been very few Indian cases on land throughout the campaign.

The services of the chemical analyst were called in to prove the absence of metallic poisons in the food and drinking water and the absence of arsenic in the hair of those affected.

Major Stevenson of the Central Laboratory in his investigation noted that the same regiment had had one or two similar cases at another camp during the previous spring: also that 7 of the men affected had been in Mesopotamia only between 42 and 48 days. These 7 cases had arrived in Mesopotamia from a dépôt in India, where they had been for over a year. The voyage from Bombay to Busra takes less than a week, so that the length of the period on board ship cannot be a factor in causing the disease. Some of the remaining cases had come direct from the United Kingdom to Mesopotamia and had been in the country several months. One of the 7 recent arrivals was the case Pte. P., mentioned above.

This is an important point because three months of a deficient diet has been mentioned (5) as the minimum period before the beri-beri syndrome will manifest itself: note the typical cases described below under C where five months of the deficient ship rations were necessary.

Major Stevenson also drew up a plan of the sixty tents occupied by the regiment and marked in the cases per tent. The essentials of his plan are reproduced here as Fig. 1. It will be seen that the machine-gun section had more than its share of cases: moreover some of the earliest cases came from this section.

Major Stevenson also calculated by the Laws of Probability what the tent

distribution of these cases would be, if among all the occupants of these sixty tents there were an equal chance of the disease occurring; as, for instance, would be the case were the whole regiment equally exposed to some virus. According to this calculation:

23	tents	would	have	no cases
22	„	„	„	1 case
10·5	„	„	„	2 cases
3·3	„	„	„	3 cases
0·5	„	„	„	4 cases.

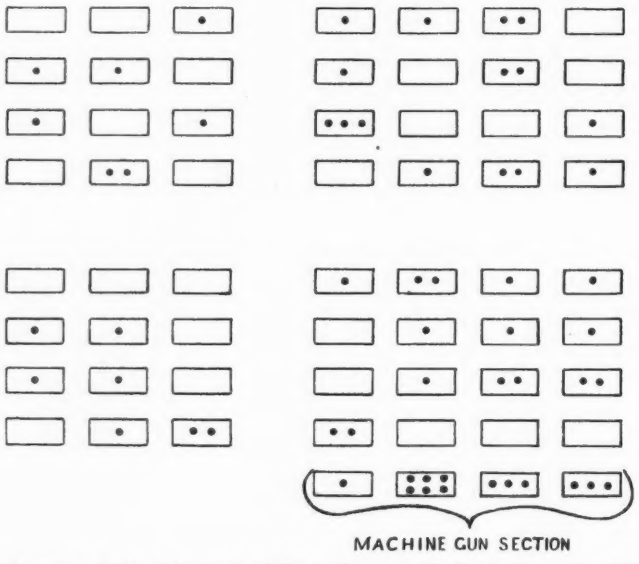

FIG. 1. Diagram of the sixty tents of the regiment at Shaiba in December 1916. Each black dot represents a case diagnosed as beri-beri at the time of the epidemic.

The actual figures were:

23	tents	had	no	cases
24	„	„	1	case
9	„	„	2	cases
3	„	„	3	cases
1	„	„	4	cases.

These actual and calculated figures correspond so closely as to be strongly suggestive of an equal distribution. But that is only if we consider the whole sixty tents as one unit. It is possible, on the other hand, to regard the more heavily affected machine-gun section as a separate unit. In that case the machine-gun section might be considered as the starting-point of an infection that spread equally among the rest of the regiment. Major Stevenson also made very thorough inquiries into the diet of the regiment. There seem to have been no defects except that the amount of total solids in the Shaiba water was so high as

to necessitate prolonged cooking of stews. An ordinary stew seems to have taken five hours to be palatable, whilst dhal never became soft enough to eat. The oatmeal in bags was weevily and therefore unpopular, so latterly tinned oatmeal was supplied, and this was satisfactory. Practically no rice seems to have been eaten.

Major Stevenson did blood cultures on eleven cases of this type under aerobic and anaerobic conditions: they were negative. The dietary deficiencies mentioned were with some likelihood considered at first to be responsible for the disease; but Major Stevenson subsequently considered it probable that an infective agent was at work. The deficiency theory certainly receives a severe blow when we come to the recurrence of the disease in the same regiment a year later at Nasiriyeh.

Colonel Melville and Major Stevenson also investigated this second epidemic, and I have had the advantage of discussing it with Captain Ford, the officer then in medical charge of the regiment. There were fourteen cases this time, all of the same type as in the preceding year. Two of the cases had been in the country only nine and ten weeks respectively, and the latter of these two came direct from England, the former from a dépôt in India.

Neither of the investigating officers was able to find any deficiency in the dietary: in fact owing to the occurrence of the disease in the previous year special care was taken to see that the men's food was satisfactory. The oatmeal was now clean and the water good, and Captain Ford was satisfied there was nothing lacking. Certainly the battalion had whatever the rest of the Force was getting and in some cases more. There was very little beer available, and three of those affected were total abstainers. Eggs, notably rich in vitamines, were occasionally eaten: one of the patients ate four eggs a week. In addition, from November 1, the whole battalion had been on marmite, ¼ oz. per man twice a week.

Major Stevenson investigated more thoroughly eight of the cases which were selected by Colonel Melville as the most typical. Two of these eight cases were recrudescences from the previous year's attack: it is remarked below concerning the Chinese cases how prone those who have once suffered from beri-beri are to relapse. Major Stevenson also made a spot map of the distribution of these eight cases amongst the regimental huts: the total number of huts was about fifty. He found that:

2 cases occurred in 1 hut in 3 instances
and 1 case „ „ 1 „ „ 2 „

Each of the two recurrent cases had a fresh case in the same hut with him. He concluded that this was not a 'chance' distribution. It would seem, however, that the numbers are too small here to make a deduction of value.

Amongst the total fourteen cases there was a history of recent diarrhoea in two, and of dysentery in one case. The incidence of dysentery had been high during the preceding two months in all units in Nasiriyeh, and a little higher in

the beri-beri infected regiment than amongst other British units there. Stool cultures by Major Stevenson of his eight selected cases and of cases of dysentery in the battalion gave no information. Neither did the plating out of the next 100 consecutive cases of enteritis in the regiment. The differential leucocyte counts of seven affected cases were normal; blood cultures in the seven cases were sterile except for a few contaminations.

Three of the cases gave a recent history of tonsillitis. Swabs from the tonsils of eight tonsillitis cases (not with neuritis) in the battalion were also plated out: no diphtheroid organisms were found. This finding is of importance because about a year later there were three cases of post-diphtheritic palsy in this regiment after it had moved to a distant camp. The suggestion was then made that the epidemic of the two previous years had been diphtheritic, but this idea cannot be held because the paralyses were of a different type: there was no ocular or palatal palsy in the 1916 or 1917 epidemic. Also it would be incredible that sixty-six cases of post-diphtheritic palsy could occur in one year and fourteen in the next, all of the same type, and without any diphtheritic throats in the battalion. The investigation of this second or Nasiriyeh epidemic confirmed Major Stevenson in his opinion that the 'disease was not due to a food deficiency, but was a neuritis sequent to a toxic or infective factor'.

The recurrence at Nasiriyeh seems to have shaken Colonel Melville's original opinion regarding the Shaiba epidemic, since he reported: 'The presence of the disease again this year in a body of men, specially dieted and looked after—at the same time of the year and in another station—is rather striking and suggests some cause other than purely dietary.'

Another unit had also an undue number of cases with the same cardio-neurotoxic syndrome as described above. This unit was not a homogeneous one, being composed of men from numerous outside units, collected together at the Base and employed on clerical duties only. In this unit there has been no epidemic; but at various times during the two years ending with November 1918, fifteen cases have occurred out of a total of about 700 men. No case has occurred since November 1918. These men are sedentarily employed, and are on the same rations as the rest of the British troops at the Base. The occurrence is suggested of some source of infection in the unit during this period. Sporadic cases have also occurred in the Force.

Exclusive of the epidemic already described in the regiment, there were reported eighteen cases during 1917, and thirty-seven cases during 1918. At least four of these cases were officers, in only one of whom was there any suspicion of his having been on a shortage of anti-beri-beri vitamines at any time previously. One sees not rarely in Indian civil practice cases of leg polyneuritis that one can hardly explain by diet deficiency or other known cause. Sir John Rose Bradford, in a recent paper (6) on polyneuritis, writes of seeing occasionally similar cases on the Western front, which he regarded as milder manifestations of a specific infective febrile polyneuritis. The cases the writer has seen have also not uncommonly been associated with slight febrile disturbance; but he has only rarely

seen the more severe polyneuritis to which Sir John Rose Bradford refers as the standard type. The cardiac disturbance was not a frequent feature of his cases; so the infective agent, if any, in the Mesopotamian cases may not be the specific organism isolated from Sir John Rose Bradford's cases. Epidemics of similar polyneuritis have occurred in British regiments before, notably in the Royal Lancaster regiment at Lebong (7) in 1914, and in the King's Own Scottish Borderers at Aden (8) in 1907.

It seems, therefore, probable that a cardio-neurotoxic syndrome, apparently identical with that known as beri-beri, can occur apart from any deficiency of diet; and the probability is that it is a result of infection by some micro-organism. There is no evidence yet how infection occurs; the intestinal route is suggested by the occasional clinical association with enteritis as well as by the well-known post-mortem finding of duodenitis in both human and avian cases.

B. *Beri-beri amongst the Chinese in Mesopotamia.*

A Chinese Porter Corps from Singapore arrived in Busra in 1917. The corps came in two drafts, the first in January and the second in April. Cases of beri-beri occurred in both drafts on the voyage and some of them were landed in Bombay. Beri-beri became very severe in the beginning of April and remained so for the next three months. There were 615 cases and 29 deaths from beri-beri in this unit, whose total strength was only about 1,000. Of the remainder several showed early signs of the disease. The entire unit was therefore repatriated. The diet of this corps at first was practically the same as that mentioned below as the present diet, with the exception that there was no bread supplied, 12 oz. of meat were given daily instead of 4 oz., and 28 oz. of rice instead of 20 oz. This rice was of the polished Siam variety, and had been brought with the corps from Singapore because it was their usual staple diet. No immediate successful result was obtained from the use of a diet richer in vitamines. The history of this corps does not afford us sufficient data for deductions as to the origin of the disease. The diet may well have been defective; but beri-beri was evidently established in the corps when it sailed from Singapore. In this case the great majority of the cases occurred between the beginning of April and the end of June, which is contrary to the experience given below with the other Chinese labourers. But in the case of the Porter Corps there were exceptional factors. A possible recent deficiency in their diet is not denied, as it is in the case of the dock labourers. The Porter Corps had only just landed and had been on this possibly deficient diet during the voyage and for some weeks after landing. Moreover in the light of what is said below it may be stated here that the rainfall in the winter of 1916–17 was almost negligible and the following spring correspondingly hot and dry.

Other Chinese labourers have, however, been employed and have been under observation for longer periods.

Some thousands of skilled Chinese labourers, for the most part fitters, boiler-makers, riveters, hammermen, and carpenters, have been brought into Mesopotamia since the summer of 1917 for work in the dockyards and railway workshops. Since the spring of 1919 the repatriation of these men has begun and their number is now under one thousand. They have shown and continue to show several cases of beri-beri, 198 in 1918 and 76 cases up to the end of September 1919. Clinically this disease amongst them is indistinguishable from the cardio-neurotoxic syndrome above described as occurring amongst British soldiers.

The common complaint of the Chinaman with beri-beri is of the heaviness of his legs and of their weakness: often also he remarks on the flabbiness of his calves. On admission to hospital he usually has a temperature of about 100° F., and this pyrexia lasts three or four days. There is often tenderness of the calf muscles. The knee-jerks may be absent; but are more commonly exaggerated, and are often unequal. Anaesthesia in patches is often present on the legs; but this is difficult to elicit accurately in the Chinaman. Oedema over the lower parts of the shins is usually present, but soon clears with rest; this appears to have but little if any relation to the cardiac condition. There is sometimes dilatation of the left heart, and very often undue sensibility to slight exertion, a pulse of 80 accelerating to 120 or more on the patient's sitting up in bed. Cardiac bruits are often heard over mitral, tricuspid, and pulmonary areas. Examination with a differential stethoscope (Leyton's model) shows as a rule abnormality only if the examination be made in the first few days after admission. The ratio between the intensity of the sounds then sometimes indicates myocardial derangement, and in severe cases this sign may last for long.

As regards treatment rest in bed rapidly benefits all but the most acute cases: the exhibition of marmite or of other special foods seems without effect. Relapse on resuming work is very common.

A brief account of a typical case is given here.

A. Y., age 26, a boat-builder, six months in Mesopotamia, came to hospital on July 26, complaining of weakness and heaviness of his legs. He was of fair nutrition, and showed absence of knee-jerks, but had no calf-tenderness or apparent anaesthesia. There was slight oedema of the front of the lower legs. There was some dilatation of the left side of the heart, accompanied by a systolic murmur at the apex. The pulse-rate when sitting down was 116; after walking a few steps it was 146 per minute. The gait was high-stepping.

The illness was accompanied by slight pyrexia; the temperature rising to between 99° and 100° for four days, and then, after five days of being subnormal, returning to the normal.

The patient rapidly improved after a few days' rest in bed: he was, however, evacuated from the country.

Experience has shown us that cases of beri-beri, however mild, are so liable to a return of the condition, either on the resumption of hard work or from the

onset of any other disease, that it is advisable to repatriate any Chinese beri-beri case as soon as he is fit to travel. During a malaria epidemic in Busra some of the Chinese who were attacked with malaria reported sick with beri-beri symptoms: a similar combination with influenza was also sometimes seen. Any cause of debility that would produce its own train of symptoms in another subject might apparently, in one of these Chinese, produce beri-beri. An example of malaria with beri-beri is seen in the case of W. M. C., a Shanghai ship-plater, who had been in Busra eight months when he reported sick, complaining of weakness of the legs.

He showed a tertian fever with regular ague attacks, and a spleen reaching three fingers below the rib margin. The benign tertian parasite was found in the blood. He also showed signs of early beri-beri, with exaggeration of knee-jerks, oedema of the shins, and some anaesthesia of the legs. The gait was high-stepping on a broad base. From the size of the spleen he had doubtless been suffering from malaria for some time, and it is probable that the resultant debility had determined the onset of beri-beri.

A few more cases only need be referred to, to show after how brief an interval after arrival in Busra the neurotoxic syndrome may evince itself, much less than the several months of deficient diet considered necessary for the development of beri-beri in a previously healthy subject. Even if we include the period of the voyage from China the time is too short: some cases have actually been taken off the boat with the disease already manifest.

F. N. H., a moulder, reached Busra on October 6, 1918, and felt weakness of the legs seven days later: he was in hospital from October 17, and showed the usual syndrome.

S. Q. L. reached Busra on February 6, and began the disease on March 16, $1\frac{1}{3}$ months after arrival.

Stevedore B. A. L. reached Busra on September 6, and developed beri-beri on October 12, five weeks after arrival.

Other cases show intervals of 26 days, 23 days, 25 days, and 7 days respectively between disembarkation at Busra and development of beri-beri. In the case of blacksmith Y. A. S. the interval is even shorter. He left Shanghai on August 21, arrived in Busra on October 7, and developed beri-beri the next day.

If it be true, as seems the case, that three months' vitaminic deficiency are necessary for the primary development of beri-beri, then these cases, if suffering from a primary attack, must have had the disease developing before they left China. Moreover the dietaries on the ship from Shanghai to Bombay, at the camps in Singapore and Bombay where they stay *en route*, on the ship from Bombay to Busra, and in the Mesopotamian Force after arrival in Busra must also have been deficient. This is a large assumption to make. The probable explanation is that these cases had all had beri-beri previously in China, or had lived for years on a partially avitaminic diet to the extent that any hard work or general debilitating cause would bring on the cardio-neurotoxic syndrome.

A study of the cases that have arisen after several months' residence in Mesopotamia makes a similar deduction probable. There seems to be no deficiency in the diet given to the Chinese in Mesopotamia. When the first cases of beri-beri occurred much thought was given to the matter, and in consultation with the Chinese headmen a diet as rich as possible in anti-beri-beri vitamines was arranged. Money was not spared in framing this diet: salted eggs and China tea were imported, and dried beans and peas were freely given. So generous is the allowance that the food of the Chinese labourer has become more costly than that of the British soldier. This is an important economic point and a fact that deducts greatly from the value of a Chinese force. The amount of each article of diet issued daily to each Chinaman is given here. The rice is of the unpolished variety.

Chinese daily ration for week ending August 9.

Quantity of each article in ounces.

	Sunday.	Monday.	Tuesday.	Wednesday.	Thursday.	Friday.	Saturday.	
Rice	20	20	20	20	20	20	20	
	Frozen	Fresh	Frozen	Fresh	Fish	Fresh	Frozen	
Meat	4	4	4	4	6	4	4	Usually beef: pork rarely available
Wholemeal bread	4	4	4	4	4	4	4	
China tea	½	½	½	½	½	½	½	
Jam	2	2	2	2	2	2	2	
Sugar	2	2	2	2	2	2	2	
Salt	½	½	½	½	½	½	½	
Green vegetables	4	4	4	4	4	4	4	
Milk	2	2	2	2	2	2	2	
Salted eggs	—	2	—	—	2	—	2	Not by weight
Cooking oil	1	1	1	1	1	1	1	
Vinegar	1	1	1	1	1	1	1	

In some weeks potatoes are given in lieu of green vegetables; also peas or beans: and salt fish or bacon may be given in lieu of salted eggs.

In addition to the above the Chinaman spends his own liberal pay readily on the purchase of extras. He is especially fond of prawns, ducks, fowls, vegetables, pickles, and green peas, fresh or tinned, and supplements his already adequate rations with these. It does not seem therefore that any present or recent vitamine deficiency is the cause of the Chinese beri-beri in Mesopotamia. On a few occasions the number of cases occurring at one time has been of the nature of a mild epidemic and has led to special inquiry. There was a small outbreak at Amara in October and November 1918. The writer investigated this together with the local officers and could find no vitaminic deficiency. The incidence of the disease was heaviest amongst the boiler-makers.

The cases that occurred in November appeared to be strangely grouped at one end of the Chinese living hut, vide Fig. 2.

A similar tendency to grouping in certain huts is shown in the cases that were occurring in the dockyard huts at Busra, also in November 1918, vide Fig. 3.

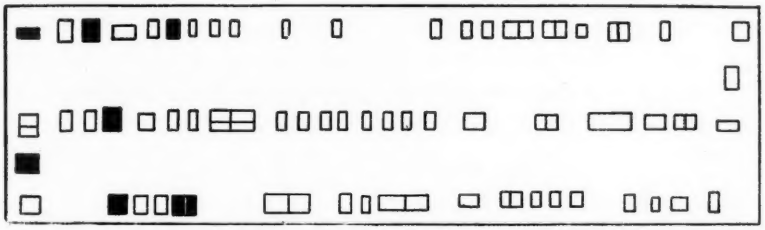

FIG. 2. Diagram of the beds in the Chinese hut at Amara in November 1918. Each bed marked in black represents where a man slept who developed beri-beri. 75 beds altogether: 8 cases. Not drawn to scale.

The diagrams are presented here because they appear of interest; but the writer cannot adequately explain them. The arrangement is not definite enough to warrant the deduction of an infective agent being at work. Moreover there were prepared an equal number of diagrams of other areas that show a 'scatter' or 'chance' distribution. Captain Mitra, I. M. S., in medical charge of the Busra dockyard, prepared the Busra diagrams, and further he made an interesting experiment to see if the disease tended to linger in the buildings themselves. He evacuated the most infected huts (shown in Fig. 3) of Chinese labourers, and then, without taking any sanitary measures with regard to the buildings or their surroundings, he put Indians into them. No case of beri-beri has occurred amongst these Indians in the course of a year.

The disease tends to occur more in the autumn; and this seems the case also with the British troops in Class A. The following statement shows approximately the average strength of Chinese in Mesopotamia, the exact number of beri-beri cases, and the morbidity percentage calculated therefrom in the course of thirteen months for which these figures are available:

	Chinese.	Chinese beri-beri cases.	Morbidity rate per cent.
1918			
September	5000	13	0·26
October	5000	33	0·66
November	5000	42	0·84
December	5000	13	0·26
1919			
January	5500	15	0·27
February	5700	8	0·14
March	6000	12	0·20
April	5000	10	0·20
May	4000	2	0·05
June	1800	4	0·22
July	1430	5	0·34
August	1260	8	0·63
September	1190	12	1·00

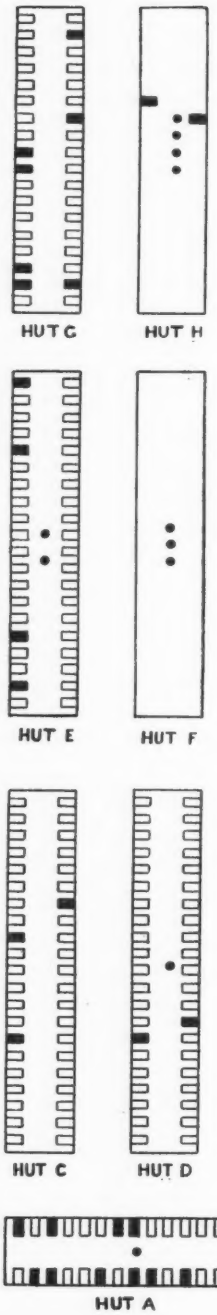

FIG. 3. Diagram of some of the huts of the Chinese labourers in the dockyard at Busra in November 1918. Not drawn to scale. Beds marked in black are those whose occupants became affected with beri-beri in the three months preceding. Cases whose bed cannot be located are marked by black dots in the centre of the hut.

Hut	A	28	men	11 cases
,,	B	36	,,	13 ,,
,,	C	42	,,	3 ,,
,,	D	42	,,	3 ,,
,,	E	40	,,	6 ,,
,,	F	40	,,	3 ,,
,,	G	36	,,	7 ,,
,,	H	36	,,	6 ,,

If one may make deductions from a statement of this kind, it would seem that external temperature has no influence on the disease. Though the incidence is at its minimum when the weather begins to grow hot, yet it commences to increase during the hottest month, and increases still more as the weather grows cool, to decrease suddenly in the coldest months. The only weather factor in Mesopotamia that corresponds with this change is the rain. Rain usually ceases in Mesopotamia in April, and after six rainless months the wet season begins in late November. In 1919 occasional falls of rain continued till May, and the rainless period in this case corresponds therefore with that during which there is a gradual increase in the beri-beri incidence.

Too much importance must not, however, be attached to limited observations of this nature.

The outbreaks referred to in October and November 1918 were in Amara and Busra; also in October a small outbreak occurred amongst the Chinese at Shaiba. This is the same Shaiba where the epidemic occurred in the British regiment in 1916, but the actual sites were nearly two miles apart. The writer investigated this Chinese outbreak on November 1. The distribution of cases amongst the dwelling huts was of the 'scatter' type. There were deficiencies in the diet in that the dried peas were heavily infected with a small beetle and almost uneatable, and the flour was white, i. e. not wholemeal; but there appeared to be no gross lack of vitamines. The rice, which forms the principal article of diet, was of the unpolished variety. The following extract from the writer's report at the time will serve here:

'The disease was said to have begun in Shaiba during June last, but it was getting worse latterly and about half the cases occurred during the last month. Besides the 17 cases I saw, since June 9 beri-beri cases had died, 8 had been sent to India, and 7 more were now in No. — I. G. H. at Busra.'

This makes a total of 41 cases in five months amongst a total Chinese population of 280; that is, a case incidence of 14·6 per cent. The 280 Chinese may for practical purposes be divided into three batches; 140 men from Shanghai, who arrived in Mesopotamia on May 3, 1918, 100 men from Chi-li, who arrived in Mesopotamia on June 20, 1918, 40 men from Canton and Singapore, who arrived in Mesopotamia on February 9, 1918.

The incidence of the disease has not been equal in these three batches; thus:

	Total No. of men.	No. of cases.	Percentage of cases to healthy.
Shanghai	140	22	15·7
Chi-li	100	4	4·0
Canton and Singapore	40	15	37·5

The men who have been in Shaiba the longest are thus seen to be the worst affected.

Neither is the occupation incidence equal:

	Total No.	No. of cases.	Percentage of beri-beri cases to healthy.
Boiler-makers	40	12	30·0
Fitters	150	14	9·3
Riveters	30	6	20·0
Hammermen	40	5	12·5
Turners	8	3	Numbers too small
Carpenters	2	1	
Tinsmiths	10	0	

From this it is seen that the boiler-makers have the highest incidence, a fact I also found in investigating a similar epidemic amongst the Chinese in Amara. The boiler-makers probably have the hardest work of any of the above. It may be added that after reduction of the working time from nine to seven hours daily, accompanied by rectification of the dietary deficiencies mentioned, there were no more cases of beri-beri at Shaiba.

The experience of the Mesopotamian Force with Chinese labour is not an isolated one in the war. Three French observers give an account (9) of 228 cases of beri-beri amongst the Indo-Chinese at Marseilles. They say that most of the cases developed before disembarkation or within a few days after. Another French medical officer in Algeria writes (10) of 251 cases of beri-beri amongst Annamites imported during the war. He attributes the outbreak to overcrowding on the transport, and could find no evidence of food insufficiency.

To sum up, the exciting cause of an attack of beri-beri in a Chinaman in Mesopotamia appears to have been fatigue, or the onset of any other illness or general debilitating factor. But there is a predisposing cause of long standing, and affecting much of the young manhood of Eastern Asia to an extent that detracts from its economic and military value. This cause appears to be latent beri-beri previously acquired in the man's own country. The ultimate cause of this latent beri-beri may be a vitaminic deficiency of long standing: it may be an infection like that which is thought to occur in the British cases.

C. *Ship Beri-beri in Mesopotamia.*

The ship beri-beri that has occurred in the Mesopotamian campaign, though clinically resembling the two forms previously described, has been apparently of a different origin and certainly much easier to deal with. We have here the classical disease due to a food deficiency, taking five months of this deficiency to evince itself and cured by remedying the defects in the diet. This may be regarded as 'primary beri-beri' in contrast to the latent or secondary form from which the Chinese suffered. There were two small outbreaks of this primary beri-beri amongst Indian crews on boats at the bar where the Shat-el-Arab flows into the Persian Gulf. The first of these was in December 1916 on the ship C. and was investigated by Lt.-Col. Melville, I. M. S., then Consulting Physician at the Base. There were four cases of beri-beri amongst an Indian crew of forty-two. Most of the crew had been on the ship for three years; some

had been there seven months, none for a less period. The ship C. had been on the bar for just over five months, and only since that period had there been difficulty with the rations. Fresh food, except fresh meat, was not common, since a month's rations were put on board at a time. The staple food was rice, and this was of the polished white variety. Atta (wholemeal flour) was supplied, but only rarely eaten. The dhal (pulse) ration, which might be expected to replace vitamines deficient elsewhere, was somewhat short, and the variety supplied was so difficult to soften in water that it was often discarded. Colonel Melville considered there was evidence of a vitamine shortage and that the beri-beri was due thereto. The diet was corrected and no further cases were reported. The second outbreak occurred in October 1918, on the ship S. M. also at the bar, and was investigated by the writer. As in the ship C. the clinical features were more cardiac than neurotoxic; dilatation of the heart and tachycardia with slight oedema of the shins were always present. In some cases the knee-jerks were exaggerated; in only one, who died, were they absent.

The crew of eighty-one men had been on the ship S. M. for six months, and there were altogether seventeen cases of beri-beri. Amongst the eight cases the writer saw personally, in four the syndrome had taken five months and in four others six months of service on the ship to appear.

The incidence of the disease amongst the crew was as follows:

	Total No. of men.	No. of beri-beri cases.	Morbidity percentage.	Deaths.
Europeans	21	Nil	—	—
Indians.				
Hindus	28	14	50·0	5
Mohammedans	20	3	15·0	—
Goanese	12	Nil	—	—
Total	81	17	21·0	5

The Goanese ate European rations: no one on European rations got beri-beri. The lower morbidity amongst the Mohammedans is probably because ten days previous to the medical inquiry the captain of the ship read that the disease was due to food deficiency, and then tried to put the Indian crew on European rations. The Hindus, however, refused to take them and kept to their former food. The Mohammedans had no scruples. Previously to that time both Hindus and Mohammedans had been on the same rations. These rations on examination, though abundant in quantity, were evidently deficient in anti-beri-beri vitamines. The rice was of the polished or Rangoon variety. The flour was white (i. e. not wholemeal); it was also weevily. The dhal, which might have supplied the defects of the rice, was very dirty, containing many moth eggs and maggots. These defects were remedied in various ways, and the captain of the ship wrote some months later that he had had no further cases of beri-beri.

These two outbreaks of ship beri-beri appear therefore to be due to food deficiency.

Clinically the resemblance between the above three classes is great. Any one case might have occurred in any of the three classes. When considered *in toto*, however, Class A may be said to have the nervous more in evidence than the cardiac symptoms; Class C has the cardiac symptoms more prominent; while Class B is intermediate between these two and usually has both nervous and cardiac symptoms. Oedema over the lower shins is present in only a proportion of the cases of Class A; it seems always to be present in Class C, and usual in Class B. Having regard to McCarrison's discovery of the extensive endocrine changes in birds fed on decorticated rice, the liability of the Chinese cases to recurrence as a result of an outside depressing factor is somewhat suggestive of a chronic endocrine deficiency. That endocrine changes occur has also been shown by Seishichi Ohno (11), who finds an hypertrophy of suprarenal medulla in beri-beri cadavers. This agrees with McCarrison's observations on underfed birds, and is also in accordance with post-mortem appearances the writer has seen in emaciated prisoners of war with so-called war oedema. Several Turkish soldiers, when captured by us in 1918, were in this condition, and some showed post-mortem suprarenal hypertrophy.

The idea that beri-beri is due to a food deficiency and to nothing else has of recent years been too dogmatically stated. Drs. Harriette Chick and Margaret Hume begin their paper (12) on 'The Distribution among Food-stuffs of the Substances required for the Prevention of Beri-beri and Scurvy', by saying, 'Sufficient evidence is now available to permit beri-beri . . . to be classed among the "deficiency" diseases due to a defective diet, without further comment.' Similarly a recent lecturer (13) states: 'Beri-beri is a deficiency disease, due to reliance upon polished rice': like statements have also been made by leading physiologists (14 and 2). The numerous medical officers who have worked in Mesopotamia during the last three years arrived in the country imbued with that teaching. Many of them have come in contact with British or Chinese cases and tried to reconcile their previous teaching with the facts as described here and with the conditions under which these cases have arisen. This they have been unable to do, and many have left Mesopotamia with the impression that the accepted theories as to the causation of beri-beri are incomplete.

This paper states the principal facts of a Mesopotamian experience, and attempts to reconcile them with previous clinical observations and animal experiments. There are still difficulties in our entire understanding of the subject; but the comparison of the various conditions under which beri-beri has arisen in the Mesopotamian campaign will help, the writer hopes, to throw some light on the origin of the disease, and to explain some of the apparent contradictions that medical officers have been faced with.

Summary.

The disease called beri-beri is a syndrome which may arise from various causes under different circumstances. One class of case is not due to a food deficiency; but appears to result from an infection. Other cases are due to a vitamine deficiency in the food: this takes a few months to operate in a previously healthy subject and may be called 'primary beri-beri'.

In yet another class the syndrome arises apparently from the effect of some depressing influence or secondary infection on a subject previously rendered susceptible to the disease. These cases may be considered to have been suffering from 'latent beri-beri'. In all classes the clinical appearance is approximately the same, there being differences only in the relative frequency of various manifestations in the three groups.

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Col. A. Balfour, C.B., C.M.G., A.M.S.
Lt.-Col. G. S. Buchanan, C.B., R.A.M.C.
Lt.-Col. H. G. Ledingham, C.M.G., R.A.M.C.
Col. C. M. Wenyon, C.M.G., C.B.E., A.M.S.

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ON THE RECTAL ABSORPTION OF GLUCOSE

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Introductory remarks. The value of rectal injections of glucose in saline has always been a matter of controversy, owing to the many doubts expressed as to the power of the rectum to absorb either this or other substances efficiently.

The frequency with which such injections are made use of in practice, however, makes it manifestly important to obtain some definite information on the subject, since, particularly in cases of functional and post-operative vomiting, its employment is the usual procedure.

The work of Ornstein (1), who adopted the washing out method in his investigations on rectal feeding in dogs, showed that at least some absorption must take place; he states, moreover, that glucose given with starch is completely absorbed.

Further Nagel (2), in his handbook, quotes the patients of Czerny and Latschenberger in whom the large intestine, or part of it, had been completely cut off from the small intestine. In such cases, and also in the dogs of Heile, which had been especially operated on for this purpose, he points out that glucose was shown to be absorbed. This author also draws attention to the work of Schönborn, who alleged that a glycosuria could be produced by injections of glucose per rectum.

Approaching the matter from a different standpoint, Reach (3) investigated the change in respiratory quotients after rectal injections of glucose, and came to the conclusion that absorption took place, slow though it was.

Despite all this, however, our knowledge on the subject is far less exact and the literature much less complete than is the case regarding the absorptive powers of the other portions of the intestinal tract, particularly in human beings. In view of these facts and the very great clinical importance of the subject, the following investigation on patients was undertaken with a view to eliciting further information and amplifying our data in this matter.

The object of the following experiments was to detect any absorption taking place by an analysis of the blood, a direct measurement in the rise of blood-sugar being made after an injection of glucose per rectum. Information as to the amount of this rise and the time of its occurrence was also sought.

Method adopted. The method used for estimating the blood sugar was that

of Maclean (4). This has the advantage of extreme facility for clinical work, and an accuracy as shown by de Wesselow (5) to be greater than the Benedict picric acid method, in which other substances such as creatinin are also estimated, as well as the sugar.

Sixty grammes of solid glucose were dissolved and made up to about 180 c.c. with normal saline. This was injected slowly into the rectum in the same manner as that used in ordinary rectal feeding. About ten minutes were taken over this injection; it was given in a single dose. Although of high concentration, the amount of fluid was so small that it was considered that the injection would be well retained and give rise to no irritation. This proved to be the case. A sample of blood was taken from the patient before the injection and at set intervals afterwards, the sugar content of the blood being estimated in each sample.

Twenty minutes following the injection was found to be too soon to show any appreciable rise, so that half an hour was adopted. Half-hourly samples were then taken up to the end of three hours, and in view of the slowness of the absorption, a final sample at the end of the fourth hour. In the first two experiments no sample was taken after the third hour, but as the blood sugar had not then settled down, in later experiments a further sample was taken as stated above.

Only those cases in which it was known that the rectum was normal were selected for the experiments.

The blood, 0·2 c.c., was obtained from the finger, the whole procedure being carried out as described by Maclean (4).

In two cases the injection was not retained, and in a third a feeling of discomfort was at first produced giving rise to the ejection of a small quantity, which, however, was so insignificant as not to interfere with the experiment.

The experiments. The experiments detailed below are not necessarily given in the order in which they were carried out, but grouped in the best way for comparison.

Experiment I. Nov. 6, 1919.

M. B. Female. Age 41. Normal.

		% glucose in the blood.
Blood sugar immediately before injection	=	0·094
Injection at 10.55 a.m.		
Blood sugar 30 min. after injection (11.25)	=	0·105
" " 55 " " " (11.50)	=	0·109
" " 1 hr. 40 " " " (12.35)	=	0·112

This shows a rise of 0·018 % at the end of 1 hr. 40 min.

Experiment II. Nov. 15, 1919.

J. M. Female. Age 30.

The patient was a case of functional vomiting, and the low blood sugar at the commencement of the experiment is therefore probably accounted for by this.

		% glucose in the blood.
Blood sugar immediately before injection	=	0·044
Injection at 11.0 a.m.		
Blood sugar 20 min. after injection (11.20)	=	0·044
„ „ 40 „ „ „ (11.40)	=	0·081
„ „ 1 hr. 40 „ „ „ (12.40)	=	0·125
„ „ 2 „ 5 „ „ „ (1.5)	=	0·078
„ „ 2 „ 50 „ „ „ (1.50)	=	0·071

This shows a rise of 0·081 % in 1 hr. 40 min.

Experiment III. Nov. 20, 1919.

E. S. Female. Age 38. Normal. Injection ejected in half an hour.

		% glucose in the blood.
Blood sugar immediately before injection	=	0·112
Injection at 10.55 a.m.		
Blood sugar 25 min. after injection (11.20)	=	0·123

This shows a rise of 0·011 % in 25 min.

Experiment IV. Nov. 27, 1919.

J. L. Female. Age 41. Normal.

		% glucose in the blood.
Blood sugar immediately before injection	=	0·088
Injection at 11.0 a.m.		
Blood sugar 40 min. after injection (11.40)	=	0·090
„ „ 1 hr. 15 „ „ „ (12.15)	=	0·150
„ „ 1 „ 45 „ „ „ (12.45)	=	0·096
„ „ 2 „ 15 „ „ „ (1.15)	=	0·090
„ „ 2 „ 45 „ „ „ (1.45)	=	0·078
„ „ 4 „ „ „ (3.0)	=	0·088

This shows a rise of 0·062 % in 1 hr. 15 min. (see Chart 1).

The fall below normal which occurs after the rise, and is marked in this and other experiments, is also often found to occur in experiments where carbohydrate is taken per os.

Experiment V. Dec. 18, 1919.

E. B. Male. Age 46. Normal.

		% glucose in the blood.
Blood sugar immediately before injection	=	0·112
Injection at 11.0 a.m.		
Blood sugar 35 min. after injection (11.35)	=	0·130
„ „ 1 hr. „ „ (12·0)	=	0·138
„ „ 1 „ 30 „ „ „ (12.30)	=	0·116
„ „ 2 „ „ „ (1.0)	=	0·104
„ „ 2 „ 30 „ „ „ (1.30)	=	0·094
„ „ 3 „ „ „ (2.0)	=	0·100
„ „ 4 „ „ „ (3.0)	=	0·112

This shows a rise of 0·026 % in 1 hr. (see Chart 2).

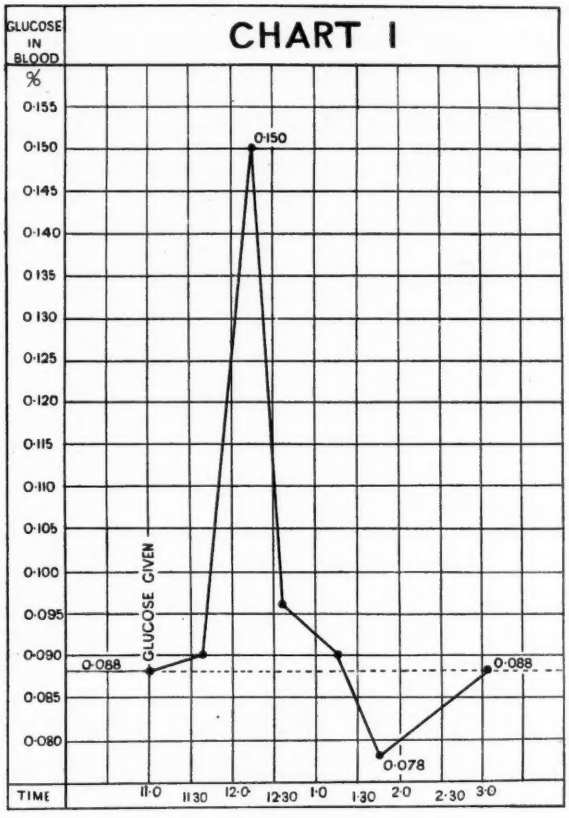
CHART 1
GLUCOSE IN BLOOD
%
0·155
0·150
0·145
0·140
0·135
0·130
0·125
0·120
0·115
0·110
0·105
0·100
0·095
0·090
0·085
0·080
0·150
0·088
GLUCOSE GIVEN
0·088
0·078
TIME
11·0
11·30
12·0
12·30
1·0
1·30
2·0
2·30
3·0

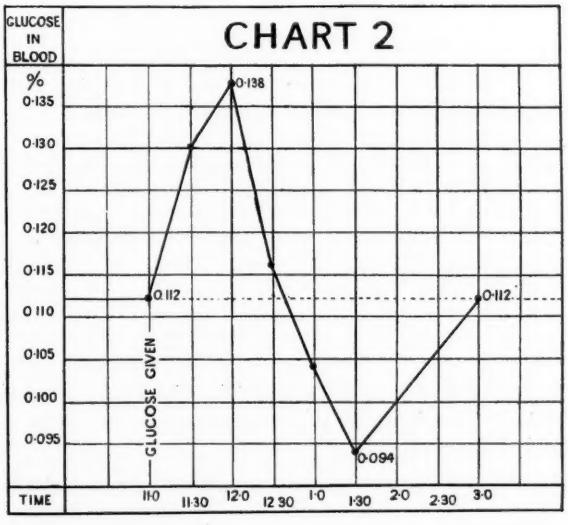
CHART 2
GLUCOSE IN BLOOD
%
0·135
0·130
0·125
0·120
0·115
0·110
0·105
0·100
0·095
0·138
0·112
GLUCOSE GIVEN
0·112
0·094
TIME
11·0
11·30
12·0
12·30
1·0
1·30
2·0
2·30
3·0

Experiment VI. Dec. 13, 1919.

S. C. Male. Age 30. Normal.

	% glucose in the blood.
Blood sugar immediately before injection	= 0·094
Injection at 11.0 a.m.	
Blood sugar 30 min. after injection (11.30)	= 0·087
„ „ 1 hr. „ „ (12.0)	= 0·097
„ „ 1 „ 30 „ „ „ (12.30)	= 0·094
„ „ 2 „ 30 „ „ „ (1.30)	= 0·071
„ „ 3 „ „ „ (2.0)	= 0·086
„ „ 4 „ „ „ (3.0)	= 0·088

This shows a rise of 0·003 % in 1 hr.

Experiment VII. Jan. 8, 1920.

W. A. Male. Age 27. Normal.

	% glucose in the blood.
Blood sugar immediately before injection	= 0·116
Injection at 11.0 a.m.	
Blood sugar 30 min. after injection (11.30)	= 0·119
„ „ 1 hr. „ „ (12.0)	= 0·106
„ „ 1 „ 30 „ „ „ (12.30)	= 0·103
„ „ 2 „ „ „ (1·0)	= 0·103
„ „ 2 „ 30 „ „ „ (1.30)	= 0·103
„ „ 3 „ „ „ (2.0)	= 0·109

This shows a rise of 0·003 % in 30 min.

All these experiments show a definite though variable rise in the blood sugar after the injection.

In some cases absorption appears to go on so slowly that no evidence of a rise in blood sugar can be obtained. Indeed, sometimes a slight fall appears at first, as is seen in the following case.

Experiment VIII. Dec. 6, 1919.

H. M. Male. Age 13. Normal.

	% glucose in the blood.
Blood sugar immediately before injection	= 0·112
Injection at 11.10 a.m.	
Blood sugar 30 min. after injection (11.40)	= 0·106
„ „ 1 hr. „ „ (12.10)	= 0·102
„ „ 1 „ 45 „ „ „ (12.45)	= 0·100
„ „ 2 „ „ „ (1.10)	= 0·100
„ „ 2 „ 30 „ „ „ (1.40)	= 0·100
„ „ 3 „ „ „ (2.10)	= 0·106
„ „ 4 „ „ „ (3.10)	= 0·102

This shows a fall of 0·012 %.

Conclusions and remarks. The above experiments show that absorption takes place, the maximum being usually attained in about 1 hr. 20 min.; the average rise at this being 0·03 per cent.

In addition to the conclusions of Hamman and Hirschman, Maclean, in work

upon which he is at present engaged, finds that in the case of carbohydrate taken per os, the maximum rise of blood sugar occurs in about 30 min. and is a 0·05 to 0·06 per cent. increase. From this it will be seen that according to our experiments a rectal injection is absorbed, but at a much slower rate, the maximum being attained in about three times as long, and being much less marked than that which occurs when carbohydrate is taken per os. The blood sugar settles down to its normal level again when injected rectally in about 4 hrs., whereas in the experiments per os this is found to occur usually in a much shorter time. Reach (3) working on this subject also showed that the maximum rise in the respiratory quotient took place at approximately the same time as the blood sugar in our experiments was at its highest.

In the light of the above evidence the conclusion that absorption of glucose from the rectum does take place seems amply justified.

The differences of absorption noted in different cases is also referred to by von Noorden (6), and it is possible that a certain amount of break-down and decomposition of the glucose by bacteria within the rectum, differing in various cases, accounts for this. The above writer quotes Bingel as showing that a process of this kind does come into play, and it must therefore be borne in mind.

With the exception of two cases, the glucose was, as stated, well retained and no ill effects resulted; there is therefore no reason to suppose that the high concentration of glucose used had an irritating or inhibitory effect on the gut, but at the same time the concentration is probably a factor in the question of absorption. Von Leube (7) states that 300 c.c. of a 10–20 per cent. solution is the maximum of utility, while, as von Noorden (6) affirms, isotonic solutions are completely absorbed.

Though both Grützner (8) and Cannon (9) pointed out in their researches that at least a large part of the absorption of rectal injections appeared to take place in the small intestine, being driven upwards by an anti-peristalsis set up by the introduction of a solution into the rectum, their conclusions may have to be modified, since other work carried out more recently seems to point plainly to the absorptive power of the rectum itself.

Hári and Halász (10), in 1918, showed a rise in respiratory quotients following rectal injections of glucose in dogs, in which the large gut had been completely cut off from the small intestine by ligature, and state further that an actual glycosuria may be produced in these animals after feeding in this manner. The fact also that the blood sugar in most cases of ours shows a rise in 30 min., which is comparatively rapid, may also be taken as evidence of the absorptive power of the rectum itself.

The above point does not, of course, affect the value of rectal injections, but is physiologically extremely interesting.

It must also be remembered that by estimating the rise of blood sugar in the systemic circulation we are probably not arriving at the total absorption, but taken in comparison with experiments carried out in the same way on

subjects where doses of carbohydrate are given per os, we gain, nevertheless, an accurate idea of the value of rectal glucose injection.

It is quite obvious, of course, that no accurate method of estimating the total sugar absorption is applicable in the case of human beings.

It is of interest to mention here, although we have not carried out any experiments with dextrin, von Noorden (6) states that it is of the greatest value for the purpose of rectal feeding, having the advantage of not only being cheaper, but, since it is a colloid, of being able to be used in higher concentrations than glucose, while it is said to be equally efficacious.

I should like to thank Dr. Maclean for his kindly advice, and the facilities given to me for carrying out these experiments, and also to thank those members of the staff who allowed me to use patients in their wards.

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THE HEART AND ITS RHYTHM IN ACUTE RHEUMATISM

By JOHN PARKINSON, A. HOPE GOSSE, and E. B. GUNSON
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With Plate 9

The beginnings of disease which ultimately produce heart failure arise most frequently during acute rheumatism. This applies to lesions both of valves and muscle. Although rheumatic myocarditis is the foundation of so much myocardial disease, and often originates while the patient is actually under medical supervision, it must be confessed that the diagnosis of acute myocarditis during an attack of acute rheumatism is usually no more than a presumption. To assist in founding the diagnosis of myocardial invasion upon the firmer grounds of direct evidence, we have undertaken this investigation of the heart in acute rheumatism with special references to changes in its rhythm. Just as the search in the past has been largely for signs which should indicate acute valvulitis and eventual valvular disease, so now the search is for signs which should indicate acute myocarditis and eventual myocardial disease, likely to determine heart failure.

We have collected information on the nature, incidence, and significance of the acute disturbances in the myocardium observed during the course of a consecutive series of fifty cases of acute rheumatism. In addition, and to try to keep these newer findings in proper relation with the old, all the other physical signs available have been noted. It will be a prolonged and difficult task to draw sound inferences for prognosis from the signs here specially considered, and our inquiry can only be a contribution towards it.

Previous Observations.

Attention may be drawn to the rhythm of the heart during acute rheumatism by the occurrence of some irregularity or by the onset of an abnormal rhythm. These disturbances have sometimes been recorded and the published cases, presenting in our opinion sufficient graphic evidence, are here enumerated.

Cases of acute partial heart-block during rheumatic fever are reported by Butterfield (2), Christian (3), Cowan (5), Cowan, Fleming, and Kennedy (6),

Cowan, McLeod, and Paterson (7), Gallavardin and Pallasse (11), Gerhardt (12, 13), Hoffmann (16), Joachim (18, 19), Lewis (21), Lundsgaard (22), Mackenzie (23), Magnus-Alsleben (27), Naish and Kennedy (28), Peabody (32), Roth (33), and White (40).

Complete heart-block arising during rheumatic fever is rare. It is recorded by Esmein, Pezzi, and Donzelot (9), Routier (34), and Holst (17). In the case described by Pardee (31), chronic as well as acute changes were discovered in the *a.-v.* bundle at the necropsy.

Premature contractions are described and discussed by Danielopolu (8), Esmein, Pezzi, and Donzelot (9), Mackenzie (24, 25), Peabody (32), and Roth (33).

Nodal (or *a.-v.*) rhythm is reported by Belski (1), Cowan (5), Esmein, Pezzi, and Donzelot (9); and 'escape of the ventricle' by Belski (1), Naish and Kennedy (28), and Neuhof (29). Sinus arrhythmia is pictured and discussed by Hart (15).

A paroxysm of auricular fibrillation was observed by Mackenzie (26) during convalescence from acute rheumatism. Neuhof (30) describes one case and Schwensen (36) two cases showing auricular flutter, and Schott (35) a case of paroxysmal tachycardia. Sutherland (37) and Windle (41) have seen pulsus alternans during acute rheumatic carditis.

Methods of Investigation.

Fifty consecutive patients with definite acute rheumatism have been studied throughout their stay in hospital. All doubtful cases were omitted. Each was examined daily, and the rate and rhythm were observed. The conductivity time was measured on a Mackenzie polygraph, tracings being taken every day in the course of the first twenty cases of the series, and on the remaining cases (1) daily for the first two weeks, (2) on alternate days for the second two weeks, (3) on every third day for the rest of the stay in hospital. If any abnormal condition appeared, daily tracings were again taken. The average period of observation in hospital was between six and seven weeks. The relation of pyrexia to the changes in rhythm was observed and recorded upon the temperature charts. The rate of the pulse was counted daily from the tracings. Electro-cardiograms were taken from time to time. The conclusions drawn from this part of the investigation are based upon more than 1,350 polygrams and about 100 electro-cardiograms. These frequent records, even in apparently normal cases, were made so that the development of the earliest stages of acute heart-block and other arrhythmias should not be missed. The position of the apex beat and the auscultatory signs were entered in the notes on admission, and subsequently at least once a week, along with any change in other physical signs as they occurred. Discharged patients were examined at intervals of about two months until the outbreak of war caused a suspension of this part of

the work, and unfortunately the lapse of time has now rendered it impossible to trace them.

General Features.

1. *Diagnosis.* Many cases proposed for observation were rejected because the symptoms and signs were not conclusive of acute rheumatism. The cases accepted were young people with pyrexia of sudden onset and pain moving from joint to joint. In thirty-seven of the fifty cases the joints were swollen on admission; of the remaining thirteen each showed in favour of the diagnosis one or more of these evidences, namely, rheumatic nodules, pericardial effusion, mitral stenosis, aortic incompetence.

The ages varied from 4 to 35 years; in eight only was the age over 20. Thirty-six were males and fourteen females. First attacks numbered twenty-five cases.

2. *Tonsils.* There was a history of sore throat accompanying the attack in sixteen cases, and enlarged tonsils were present in thirty of the fifty patients.

3. *Glands.* Since glandular enlargement accompanies certain infections and could throw light upon the portal of infection, this condition was specially noted. In twenty-eight, rather more than half, the glands were easily felt, and were considered larger than normal in the cervical, axillary, or inguinal regions. In twenty-six of the twenty-eight cases, the cervical glands were among those affected, in ten the axillary, and in three the inguinal.

4. *Pyrexia.* Hyperpyrexia did not occur, and a study of the temperature charts revealed nothing except the possible relation of pyrexia to heart-block, a subject discussed below.

5. *Treatment.* Salicylate was administered to each patient. Varying with the age, sodium salicylate, gr. 10–20, was given two-hourly for six doses, then four-hourly for some days. Subsequently this dose was given three times daily, in most cases until discharge.

6. *Complications.* Mitral stenosis arising from previous attacks was present in four cases and aortic incompetence in seven. In some patients who had previously suffered from one or more attacks of acute rheumatism a systolic murmur was present at the apex. No attempt is made here to decide how far this indicated mitral incompetence due to a previous valvulitis. The murmurs occurring during first attacks only are discussed below.

Rheumatic nodules were found in nine of the fifty cases. Pericarditis was present in six cases. A pericardial rub, without subsequent signs of effusion, was heard in three cases, and a rub was followed by effusion in three others.

Death occurred in two cases in both of which pericarditis was present.

7. *Size of heart.* The sign used for determining changes in the size of the heart was the position of the palpable apex beat. The point accepted for this purpose was that farthest from the middle line and in the lowest space where a definite lifting impulse was felt. The results of the observations were as follows. The relative variations in position of the apex beat were seen to be

similar, whether first attacks or later attacks were analysed, and they are therefore here given for the whole fifty cases. The size of the heart during acute rheumatism and its early convalescence was increased in ten cases (20 per cent.); was decreased, compared with the size on admission, in ten cases (20 per cent.); and remained unchanged in twelve (24 per cent.). In three other cases (6 per cent.) the size increased and subsequently decreased under observation (see Summary of Cases). In the remaining fifteen of our fifty cases (30 per cent.) the apex beat could not be felt or its position was doubtful. The variation in size, when it occurred, was almost invariably slight in amount and only exceeded ½ inch (1·2 cm.) in six cases. In these the change was from one to two inches, either increase or decrease, but the clinical course presented no other common feature. Heart-block, for example, occurred in only one of them, and the variations in size among cases showing block were no different from the variations in cases without block.

8. *Murmurs.* We have dealt above with the murmurs of valvular disease of the heart indicating previous acute rheumatism. Here the murmurs present during first attacks, i.e. in twenty-five cases, are considered. In five cases a systolic murmur at the apex developed under observation, and it persisted on discharge in three of them. In sixteen cases a systolic murmur was present at the apex on admission, and in one-half of these it had disappeared before discharge. In four cases no murmurs were heard. A short apical *diastolic* murmur was heard on occasion at the apex in two cases with a normal rhythm. As a harsh systolic murmur, conducted towards the axilla, always accompanied it, mitral stenosis is the most likely explanation of the diastolic murmur. A mid-diastolic murmur was heard daily for more than a week unaccompanied by heart-block in another case with normal rhythm, suggesting that rarely this murmur can appear in the absence of block.

Although the changes in the size of the heart were considered in relation to the development of murmurs no common factor could be found. A case showing an increase in the size of the heart was no more likely to develop a systolic murmur than one which showed no increase in size. In fact, in only one of the five cases in which a systolic murmur first appeared under observation was any increase in size recorded.

Disturbances in Rate and Rhythm.

1. *Pulse-rate.* The rate usually fell with the temperature, in many cases to a low figure, 40–50 being not uncommon during the first week of freedom from pyrexia. Fig. 1 is an example of this normal rhythm at the low rate of 38, a rate, of course, quite consistent with a normal convalescence. The pulse-rate always quickened from the day when the patient began to get up, and did not return again to its very low rate. Records in all cases were taken under similar conditions with the patient lying down.

2. *Sinus arrhythmia.* Sinus arrhythmia varied much in degree and was considered to be present when the pulse intervals gradually lengthened during expiration and shortened during inspiration in such degree as could be recognized by dividers on the radial tracings. It was present at some time in all our cases, with three exceptions, Cases II, VI, and XI; in two of these the rate continued about 120 a minute. As was to be expected, while the pulse-rate was much higher than 100 a minute this arrhythmia could not always be demonstrated, although it was evident in one patient when his pulse-rate was 140. Generally when the rate returned to normal the arrhythmia became obvious and could often be recognized by palpation. Sinus arrhythmia was present in patients with aortic incompetence and mitral stenosis, indications of an infection of the heart in previous attacks. It was demonstrated on tracings taken in the presence of a pericardial rub (Cases I and XXV) and pericardial effusion (Case XXVI). What is still more significant is the fact that some degree of sinus arrhythmia occurred in conjunction with or following heart-block in each of the fifteen cases which showed block. An example of this association is shown in Fig. 2, where acute heart-block (a–c interval over $\frac{1}{5}$ sec.) is recorded with obvious sinus arrhythmia and a slow rate of 62 beats a minute. It is inferred from these findings that the presence of sinus arrhythmia does not indicate that the heart has escaped infection, recent or remote, as it is seen while the heart is undergoing infection (acute heart-block or pericarditis) as well as after the heart has been seriously affected (valvular disease). The only essential for the appearance of sinus arrhythmia in a demonstrable degree is a relative slowness of the heart-rate.

The variety of sinus arrhythmia which is independent of respiration, namely phasic variation, was observed in two cases.

3. *Premature Contractions.* (a) *Auricular.* These, the most frequent of premature beats in the series, were recorded in seven patients. The pulse-rate was usually 52–72 when they occurred, but in one case (Case I) they were present with transient pulsus alternans, at a rate of 150, and in another at a rate of 110.

Variations in a'–c' interval. (i) Among the seven cases encountered, two (Cases XXVII and XL) showed a variety of auricular premature contraction (see Fig. 3) in which the a'–c' interval was consistently $\frac{2}{5}$ sec., the premature contractions being frequent even to coupled beats, and junctional beats appearing in association. It is commonly stated that the a'–c' interval of a premature beat is increased when this is very premature, owing to the too early call on the a.-v. bundle for the passage of another impulse. This may be a frequent factor, but it is noteworthy that in both the cases with long a'–c' interval there was evidence of serious damage to the myocardium. Thus, in one of them, block had been present until four days before their appearance; in the other a short paroxysm of auricular flutter (Fig. 4), with its associated block, developed a week after the first appearance of this variety of auricular premature contraction; in some of these there was no ventricular response.

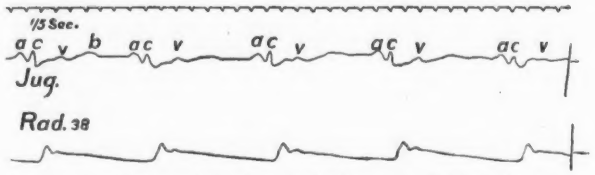

FIG. 1. A normal rhythm at the low rate of 38 a minute, during convalescence from acute rheumatism (Case XXXII).

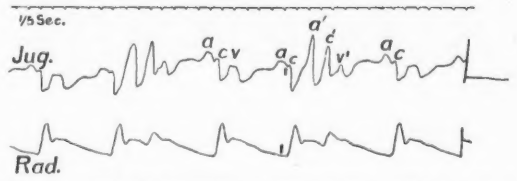

Fig. 3. Auricular premature contractions with long a'–c' interval (Case XXVII).

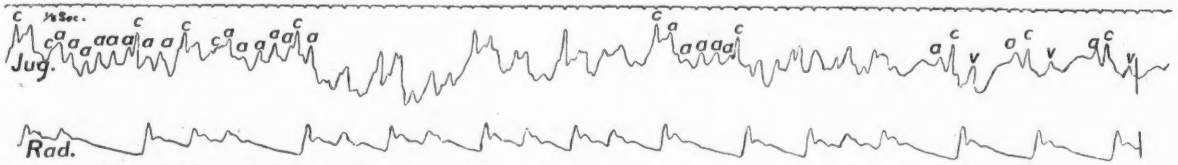

FIG. 4. Auricular flutter. The termination of a short paroxysm during acute rheumatism. The auricular (a) rate is 300 a minute, and varying a.-v. block is present. The paroxysm ends, and the last three beats are of normal rhythm (Case XL).

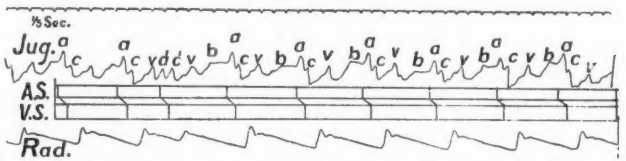

FIG. 5. Auricular premature contraction with short a'–c' interval (Case XLII).

(ii) The premature beats in the remaining five of the seven cases showed an a'–c' interval of $\frac{1}{5}$ sec. or less (see Fig. 5); they were sparse, and junctional premature contractions did not accompany them. In one of these five heart-block occurred, but not until four weeks after the premature auricular contractions were last recorded.

The time of onset was between the third and thirteenth week. In no case was pyrexia present on the days they were recorded. They persisted for two or three weeks in three cases, extending to the day of discharge in two of these, and they were present on one day only in four cases. Case XXVII was a noteworthy example of a sequence of eleven days' slight block, immediately followed by nineteen days with frequent premature auricular contractions.

The significance of auricular premature contractions in acute rheumatism. As auricular premature contractions were recorded in 14 per cent. of the cases (while ventricular occurred in 6 per cent. only), the question arises whether their appearance indicates myocardial invasion or not. Their close association with block in Case XXVII, and with auricular flutter in Case XL, suggests that they do indicate such invasion. Lea (20) watched, in a patient with mitral stenosis, auricular premature contractions give place to auricular fibrillation, and he seems to consider that such a sequence is not rare. But Mackenzie (25) states that their significance in acute infections has not so far been established, sufficient cases not having been followed.

As acute rheumatism is the commonest primary cause of auricular diseases, such as fibrillation and flutter, the appearance of premature auricular contractions in large numbers for the first time during that infection is likely to prove an indication of acute myocarditis.

(b) *Ventricular.* These occurred in three cases aged 16, 20, and 25, where they were few in number and present on one or two days only in each case.

(c) *Junctional.* In the two cases already described as presenting a special variety of premature auricular contractions with long a'–c' interval, junctional premature contractions were seen.

Salicylate and premature contractions. While certain drugs are known to produce premature contractions, salicylate seldom if ever does so. The rare variety of coupled rhythm ascribed by Danielopolu (8) to salicylate of soda is not necessarily due to that drug, for the present writers have electro-cardiographic records of a similar combination of ordinary and blocked premature auricular contractions in two cases without acute rheumatism and where salicylate had not been given. Moreover, in a case described by Esmein and others (9), frequent auricular and ventricular premature contractions occurring with acute rheumatism disappeared along with the arthritis while 90 grains (6 grm.) of sodium salicylate were still being daily administered. Similarly in Case XL of our series the premature contractions disappeared a fortnight before the salicylate (30 grains daily) was stopped.

4. *Heart-block.* Some degree of auriculo-ventricular heart-block developed in fifteen of the fifty cases (30 per cent.). Of these, eleven (22 per cent.) showed

delayed conduction in that the *a–c* interval of the jugulo-carotid tracing, or the *P–R* interval of the electro-cardiogram, became greater than $\frac{1}{5}$ sec. The increase of the *a–c* interval beyond $\frac{1}{5}$ sec. was compared in each case with the normal $\frac{1}{5}$ sec., or less, of that patient before its appearance or during convalescence. The remaining four cases (8 per cent.) showed partial heart-block with dropped beats (Fig. 6), and in one of them (Case IV) the degree of 2:1 heart-block. Case XV has been previously reported by one of us—A. H. G. (14).

No case of complete heart-block was observed. Six patients showed block during their first attack of acute rheumatism. It was present over periods varying from one to eighteen days (average nine days) and disappeared without exception before discharge from hospital, which proves that the block was a temporary event during acute rheumatism. Pyrexia accompanied the block in nine cases and was absent during the period of block in six, though in the latter, with one exception, pyrexia had preceded by a few days the onset of block. The auricular rate was more frequent during block in five cases, unchanged in nine, and less frequent in one case. In Case XXVII the period of heart-block with occasional dropped beats was immediately followed for a period of three weeks by premature auricular contractions, sometimes so frequent as every alternate beat. The onset and course of block were never betrayed by any change in symptoms.

Rate and heart-block. A prolonged *a–c* interval was recorded in cases with normal rates, even with a rate so low as 49, and when it occurred with higher rates, e.g. 120, pyrexia was associated with it. This demonstrates that while general infection with its severe symptoms is accompanied by pyrexia and a high pulse-rate, the more localized signs of the myocardial infection may quietly appear in the absence of both pyrexia and tachycardia. It may be compared with a rheumatic infection of the valves taking place while general symptoms are slight. The occurrence of block had no relation to the pulse-rate, so that frequency of pulse is not always a guide to the severity of rheumatic infection of the heart. The size of the heart was not increased with any uniformity during periods of heart-block.

Sino-auricular block. This rare arrhythmia was never recorded.

Drugs and heart-block. No patient was taking digitalis at the time of onset of block. In one case the block disappeared in spite of the administration of 15 minims of the tincture daily, started after its onset (Case XII). In the only other case in which digitalis was given block did not occur until seven days after the drug was stopped (Case I).

It has been suggested that the heart-block occurring during acute rheumatism is directly caused by the salicylate given for this disease. Several reasons may be advanced against this view. Heart-block is not a characteristic sign in fatal cases of poisoning by salicylate. If salicylate were the immediate cause of block during acute rheumatism, it would be expected when the largest doses were being given, whereas we found it more commonly during the period of small doses. We have observed the appearance, the increase, and the dis-

appearance of block during a period when 1 drachm of sodium salicylate was administered daily; on the day the block disappeared, the dose of salicylate was increased to 2 drachms daily for a week without the block recurring (Case XVI). In another case no salicylate was given during the week preceding the onset of the block, which advanced to the degree of dropped beats. The block subsequently diminished, and had entirely disappeared two days after salicylate was first administered (Case XV).

Does acute heart-block indicate acute myocarditis? In acute rheumatic carditis it is known that foci of inflammation occur in the myocardium widely, and in the *a.-v.* system. Such cases as those reported by Butterfield (2) and by Naish and Kennedy (28) correlate acute heart-block, recorded clinically, with acute rheumatic invasion of the *a.-v.* bundle found post mortem. Slight grades of chronic heart-block are common in clinical association with mitral stenosis, indicating that the block is the result of past rheumatic infection.

It is remarkable that acute block during acute rheumatism is almost always transient, disappearing during convalescence even in the rare cases of complete block. This feature is apparent in our own cases, all of which showed normal conduction again before they left the hospital. But this does not imply a functional as opposed to an organic permanent affection of the *a.-v.* bundle. It would be expected that the height of the myocarditis would be accompanied by the greatest amount of impairing infiltration, a far grosser change than would persist as the irremediable lesion. Or, as Carey Coombs (4) writes, 'The transient nature of the rheumatic heart-block . . . is perhaps partly explained by the fact that the inflammatory spot of cardiac rheumatism is in the beginning a vascular occlusion, so that to its pressure effects it adds that of a hinderer of nutrition, and recovery is in part dependent on the successful re-establishment of nutritive supply.' In any case, chronic fibrosis of some degree is a probable sequel of the inflammatory infiltration as it is in other organs similarly affected.

It is concluded that acute heart-block in acute rheumatism indicates acute myocarditis; and, of course, the fundamental question is not whether chronic partial heart-block will ensue, but whether acute changes have taken place which promise in the future other and more serious myocardial disease and consequent heart failure.

5. *Auricular fibrillation.* Although this arrhythmia is so frequent a sequel of acute rheumatism it rarely develops during the attack, and was not seen in any of our patients. Apart from Mackenzie's case (26), cases published have usually suffered from septic endocarditis complicating the rheumatic infection. In Sutherland and Coomb's case (38), the radial tracing is not completely irregular, and premature contractions offer an alternative interpretation.

6. *Auricular flutter.* The whole of a short paroxysm was recorded in Case XI in the ninth week of the disease. The clinical features will be seen in the Summary of Cases. The whole paroxysm lasted fourteen seconds and the offset is shown in Fig. 4. The tracing taken immediately before the paroxysm showed

frequent premature auricular contractions with a'–c' interval of $\frac{2}{5}$ sec., and these were repeatedly seen along with junctional premature contractions during the week preceding and the week following the paroxysm. The only subjective change during this brief attack was a feeling of discomfort in the chest with a 'lump in the throat' and a desire to swallow.

7. *Paroxysmal tachycardia.* No example of this was observed except as described under *auricular flutter.*

8. *Nodal or a.-v. rhythm, and ventricular automatism (escape of the ventricle).* Nodal rhythm was absent from our series, and we think that this diagnosis has sometimes been made in reported cases when the graphic evidence was insufficient to support it. The difficulty of the subject came to our notice when considering the tracings of Cases XXI, XLV, and L, where the rival interpretations are (1) *nodal* (or *a.-v.*) rhythm, and (2) *ventricular automatism* (escape of the ventricle). In Fig. 7 the four concluding beats show the *c* wave preceding *a*, and this coincides with the long *a*-*a* intervals accompanying expiration. These four beats are at a rate of 60 and regular, whereas in those showing a normal *a*–*c* interval the rate is 70 with a sinus irregularity. Nevertheless, we consider that the correct interpretation of the record is ventricular automatism and not nodal rhythm, because the beats showing the *c*–*a* sequence are repeated frequently in other portions of the tracing and at anticipated moments, namely, during the sinus slowing of expiration.

In Fig. 8, from Case XXI, following the first normal beat, occur eight consecutive beats with an *a*–*c* interval so short (or even a *c*–*a* interval) that one of the two interpretations under discussion must be made. During the abnormal rhythm the rate is 60 and not quite regular; when the *a*–*c* interval is normal the rate is 72 and sinus irregularity is patent. The eight abnormal beats extend over a period of two respirations, so that in this case it is not merely a momentary escape of the ventricle at the end of expiration. Yet we believe that the correct explanation of Fig. 8 is ventricular automatism and not nodal rhythm, because the interval between *a* and *c* (or *c* and *a*) varies from beat to beat as the *a* approaches, fuses with, and gradually passes *c*.

The determining factor in ventricular automatism is not exclusively the delay of the expected auricular beat. A delay as long, or even longer, in the same tracing, may be followed by a full *a*–*c* interval, i.e. no escape. Likewise, some patients present a very slow auricular rate even to 38, yet the ventricle fails to escape (Fig. 1). The other factor is probably the irritability of the *a.-v.* node, for if this is great it may precipitate ventricular escape even when the auricular rate is not specially low.

We are aware that several examples of nodal rhythm in acute rheumatism have been described. In Belski's case (1) we consider that the tracings indicate ventricular automatism, except, perhaps, his Fig. 15, which may be a nodal rhythm. In Cowan's three cases (5) the tracings of Figs. 84, 85, and 133 appear to us inconclusive; for example, in his Figs. 84 and 133 the appearance would not be inconsistent with a bifid *a*, and a normal *a*–*c* interval. Esmein,

Pezzi, and Donzelot (9) themselves admit this difficulty, and their tracings marked 'rhythme atrio-ventriculaire' seem to us no more than ventricular automatism.

That the diagnosis of nodal rhythm is not lightly to be made is clear from the convincing graphic evidence of the vagaries of ventricular automatism in recent papers by Gallavardin and others (10) and by White (39). We are unable

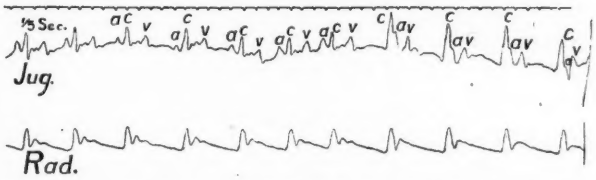

FIG. 7. Ventricular automatism. In the concluding four beats ventricular contractions (*c*) precede auricular contractions (*a*). The earlier portion shows sinus arrhythmia (Case XLV).

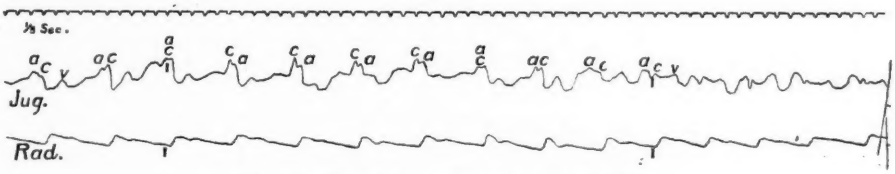

FIG. 8. Ventricular automatism (Case XXI).

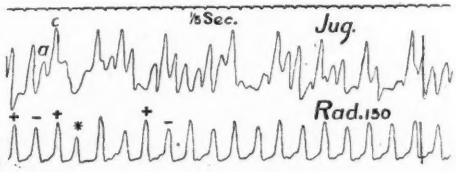

FIG. 9. Pulsus alternans, accentuated by a premature contraction (*). Pulse-rate 150 (Case I).

to accept as certain examples of nodal rhythm those above described as occurring in acute rheumatism. The diagnosis can seldom be made without electrocardiographic records, in which the inverted *P* and its unvarying time relation to *R* will establish the diagnosis.

9. *Pulsus alternans.* This was recorded in Case I during pericarditis in the fourth week of rheumatic fever (see Fig. 9). Alternation was only present on one day when the ventricular rate was 150. The *a–c* interval was then ⅕ sec., and premature auricular contractions were numerous, exaggerating the alternation.

Summary.

1. Fifty consecutive cases of acute articular rheumatism were observed with special reference to the heart and its disturbances in rate and rhythm.

2. The size of the heart, as indicated by the position of the apex beat, varied little. A change exceeding ½ inch (1·2 cm.) was only noted in six of the thirty-five cases where the apex beat was palpable. Of the thirty-five cases, the heart increased in size in ten, decreased in ten, increased then decreased in three, and remained unchanged in twelve.

The enlarged heart discovered in acute rheumatism often depends upon a complication or proves to be the sequel of a previous attack.

We conclude that the frequency and degree of enlargement of the heart during an attack of acute rheumatism have been exaggerated, and that the enlargement is usually slight when it does occur.

3. No definite relationship was found between the development of systolic murmurs at the apex and apparent enlargement of the heart. Thus, in only one of the five cases where a systolic murmur actually developed under observation was any increase in size recorded.

4. Sinus arrhythmia was present after the attack in forty-seven of the fifty cases (94 per cent.). It was demonstrated in two cases with a pericardial rub, one case with a pericardial effusion, one after auricular flutter, and in each of the fifteen cases which had developed acute heart-block. An electro-cardiogram is reproduced showing acute heart-block and sinus arrhythmia combined.

We conclude that the presence of sinus arrhythmia does not indicate that the heart has escaped infection.

5. Premature auricular contractions appeared in seven cases (14 per cent.); two types are distinguished. A paroxysm of auricular flutter was recorded in one of these cases. An irregularity observed from time to time in three patients is interpreted as ventricular automatism rather than nodal rhythm.

Auricular disease such as fibrillation and flutter is often the sequel of acute rheumatism; the frequency of auricular premature contractions in this infection, and their association with flutter and with heart-block, suggest that they indicate acute myocarditis.

6. Acute heart-block (*a.-v.*) developed in fifteen of the fifty cases (30 per cent.), proceeding to the degree of dropped beats in four (8 per cent.). It often appeared quietly in the absence of other signs, such as pyrexia and tachycardia, and it invariably disappeared during convalesence.

We conclude that acute heart-block of some grade is common in acute rheumatism; that it indicates acute myocarditis; and that it may therefore be premonitory of chronic myocarditis and eventual heart failure.

It is a pleasure to acknowledge the kindness of the Medical Staff of the London Hospital, who willingly placed patients with acute rheumatism at our disposal.

We are glad to express our sincere appreciation of the invaluable guidance and encouragement of Sir James Mackenzie, under whose direction this work was effected.

Summary of Cases.

Case I. M. M., male, aged 15. 5th attack. Observed for 99 days from 4th day of disease. Aortic incompetence. Pericarditis with effusion. *Acute heart-block* present for 12 days; *dropped beats. Premature auricular contractions. Pulsus alternans.* Apex beat not felt.

Case II. A. A., male, aged 8. 2nd attack. Observed for 77 days from 15th day of disease. Mitral stenosis. Rheumatic nodules. *Premature auricular contractions.* Apex beat not felt.

Case III. F. W., male, aged 13. 1st attack. Observed for 55 days from 8th day of disease. Swollen joints. Apex beat not felt.

Case IV. C. R., male, aged 12. 4th attack. Observed for 51 days from 9th day of disease. Mitral stenosis. Rheumatic nodules. *Acute heart-block* present for 12 days; *dropped beats.* Position of apex beat remained unchanged.

Case V. J. R., male, aged 29. 1st attack. Observed for 46 days from 6th day of disease. Swollen joints. Apex beat not felt.

Case VI. D. D., male, aged 8. 2nd attack. Observed for 90 days from 4th day of disease. Rheumatic nodules. Pericarditis. Apex beat not felt. Death.

Case VII. R. L., male, aged 12. 1st attack. Observed for 36 days from 4th day of disease. Swollen joints; rheumatic nodules. Apex beat varied in position from 2½ to 3 inches and again to 2½ inches from mid-line.

Case VIII. E. Y., female, aged 12. 1st attack. Observed for 55 days from 8th day of disease. Swollen joints. *Acute heart-block* present for 6 days; delayed conduction. Position of apex beat remained unchanged.

Case IX. T. S., male, aged 15. 4th attack. Observed for 45 days from 4th day of disease. Swollen joints. Apex beat varied from 4 to 3½ inches from mid-line.

Case X. W. S., male, aged 17. 3rd attack. Observed for 107 days from 21st day of disease. Aortic incompetence. Apex beat varied from 4 to 3½ inches from mid-line.

Case XI. L. G., female, aged 9. 2nd attack. Observed for 6 days from 40th day of disease. Aortic incompetence. Rheumatic nodules. Pericarditis. Apex beat not felt. Death.

Case XII. J. H., male, aged 11. 3rd attack. Observed for 38 days from 21st day of disease. Aortic incompetence. Swollen joints. Pericarditis. *Acute heart-block* present for 3 days; delayed conduction. Apex beat varied from 3½ to 4 inches from mid-line.

Case XIII. F. C., male, aged 8. 1st attack. Observed for 51 days from 28th day of disease. Swollen joints; rheumatic nodules. *Premature auricular contractions.* Position of apex beat remained unchanged.

Case XIV. R. F., female, aged 16. 3rd attack. Observed for 18 days from 7th day of disease. Mitral stenosis. Swollen joints. Apex beat varied from 3¾ to 3½ inches from mid-line.

Case XV. S. P., male, aged 12. 3rd attack. Observed for 56 days. Rheumatic nodules. *Acute heart-block* present for 18 days; *dropped beats.* Apex beat not felt.

Case XVI. M. M., male, aged 35. 5th attack. Observed for 32 days from 14th day of disease. Swollen joints. *Acute heart-block* present for 11 days; delayed conduction. Apex beat not felt.

Case XVII. C. B., male, aged 29. 1st attack. Observed for 64 days from 6th day of disease. Swollen joints. Apex beat varied from 4 to 6 inches and again to 4 inches from mid-line.

Case XVIII. A. B., male, aged 10. 2nd attack. Observed for 56 days from 3rd day of disease. Mitral stenosis. Apex beat varied from 2¼ to 2½ inches from mid-line.

Case XIX. J. M., male, aged 21. 2nd attack. Observed for 73 days from 5th day of disease. Swollen joints. *Acute heart-block* present for 5 days; delayed conduction. Apex beat varied from 3 to 4¼ inches and to 4 inches from mid-line.

Case XX. M. P., male, aged 15. 2nd attack. Observed for 23 days from 3rd day of disease. Swollen joints. Position of apex beat remained unchanged.

Case XXI. R. L., male, aged 22. 3rd attack. Observed for 19 days from 10th day of disease. Mitral stenosis. Swollen joints. *Acute heart-block* present for 10 days; delayed conduction. *Ventricular automatism.* Position of apex beat remained unchanged.

Case XXII. K. H., female, aged 12. 1st attack. Observed for 35 days from 4th day of disease. Swollen joints. Apex beat varied from 4½ to 3½ inches from mid-line.

Case XXIII. F. B., male, aged 10. 1st attack. Observed for 50 days from 22nd day of disease. Rheumatic nodules. Apex beat varied from 3½ to 4 inches from mid-line.

Case XXIV. R. S., male, aged 5. 1st attack. Observed for 78 days from 14th day of disease. Swollen joints. *Acute heart-block* present for 13 days; delayed conduction. Apex beat not felt.

Case XXV. A. N., male, aged 4. 1st attack. Observed for 105 days from 30th day of disease. Pericarditis with effusion. Apex beat not felt.

Case XXVI. J. O'N., male, aged 8. 1st attack. Observed for 83 days. Pericarditis with effusion. Apex beat not felt.

Case XXVII. H. G., male, aged 11. 1st attack. Observed for 35 days from 6th day of disease. Swollen joints. *Acute heart-block* for 11 days; *dropped beats. Premature auricular and junctional contractions*; *coupling.* Apex beat varied from 2½ to 3 inches from mid-line.

Case XXVIII. F. L., male, aged 20. 2nd attack. Observed for 122 days from 3rd day of disease. Aortic incompetence. Rheumatic nodules. *Acute heart-block* present for one day; delayed conduction. *Premature ventricular contractions.* Apex beat varied from 4 to 4½ inches from mid-line.

Case XXIX. J. B., male, aged 12. 1st attack. Observed for 32 days from 5th day of disease. Mitral stenosis. Swollen joints. Apex beat varied from 3 to 2½ inches from mid-line.

Case XXX. R. B., male, aged 14. 1st attack. Observed for 32 days from 32nd day of disease. Swollen joints. Apex beat varied from 2¾ to 3 inches from mid-line.

Case XXXI. T. B., male, aged 13. 1st attack. Observed for 42 days from 8th day of disease. Swollen joints. Apex beat varied from 3½ to 3¼ inches from mid-line.

Case XXXII. L. H., male, aged 34. 2nd attack. Observed for 28 days from 21st day of disease. Swollen joints. Apex beat varied from 3½ to 3 inches from mid-line.

Case XXXIII. H. E., male, aged 23. 1st attack. Observed for 52 days from 5th day of disease. Swollen joints. Apex beat varied from 3 to 4½ inches from mid-line.

Case XXXIV. J. L., male, aged 15. 1st attack. Observed for 36 days from 5th day of disease. Swollen joints. *Acute heart-block* present for 9 days; delayed conduction. Apex beat varied from 3½ to 3 inches.

Case XXXV. S. B., female, aged 13. 1st attack. Observed for 36 days from 2nd day of disease. Swollen joints. *Premature auricular contractions.* Position of apex beat remained unchanged.

Case XXXVI. B. B., male, aged 6. 1st attack. Observed for 29 days from 4th day of disease. Swollen joints. Position of apex beat remained unchanged.

Case XXXVII. D. N., female, aged 6. 2nd attack. Observed for 16 days from 7th day of disease. Swollen joints. Position of apex beat remained unchanged.

Case XXXVIII. H. H., male, aged 14. 1st attack. Observed for 14 days from 8th day of disease. Swollen joints. *Acute heart-block* present for 6 days; delayed conduction. Apex beat not felt.

Case XXXIX. N. F., female, aged 16. 3rd attack. Observed for 53 days from 4th day of disease. Aortic incompetence. Swollen joints. *Acute heart-block* present for 12 days; delayed conduction. Position of apex beat remained unchanged.

Case XL. M. G., female, aged 20. 2nd attack. Observed for 37 days from 60th day of disease. Aortic incompetence. *Auricular flutter*; *premature auricular and junctional contractions.* Position of apex beat remained unchanged.

Case XLI. A. B., female, aged 8. 1st attack. Observed for 27 days from 5th day of disease. Swollen joints. Apex beat varied from 3 to 3½ inches from mid-line.

Case XLII. B. H., female, aged 16. 2nd attack. Observed for 26 days from 60th day of disease. Swollen joints; rheumatic nodules. *Premature auricular contractions.* Apex beat varied from 2¾ to 2½ inches from mid-line.

Case XLIII. A. F., female, aged 14. 1st attack. Observed for 47 days from 5th day of disease. Swollen joints. *Acute heart-block* present for 1 day; delayed conduction. Apex beat not felt.

Case XLIV. A. L., female, aged 5. 1st attack. Observed for 35 days from 3rd day of disease. Swollen joints. Position of apex beat remained unchanged.

Case XLV. J. P., male, aged 15. 2nd attack. Observed for 49 days from 30th day of disease. Swollen joints. *Ventricular automatism.* Apex beat not felt.

Case XLVI. E. H., male, aged 8. 2nd attack. Observed for 44 days from 4th day of disease. Swollen joints. Apex beat varied from $2\frac{3}{4}$ to 3 inches from mid-line.

Case XLVII. E. M., female, aged 7. 1st attack. Observed for 42 days from 4th day of disease. Swollen joints. Position of apex beat remained unchanged.

Case XLVIII. G. D., male, aged 16. 2nd attack. Observed for 27 days from 4th day of disease. Aortic incompetence. Swollen joints. *Premature ventricular contractions.* Apex beat varied from $3\frac{3}{4}$ to 4 inches from mid-line.

Case XLIX. A. H., male, aged 25. 2nd attack. Observed for 50 days from 21st day of disease. Swollen joints. *Premature ventricular contractions.* Apex beat not felt.

Case L. H. F., male, aged 14. 1st attack. Observed for 32 days from 5th day of disease. Swollen joints. *Ventricular automatism.* Apex beat varied from $4\frac{1}{2}$ to $3\frac{1}{2}$ inches from mid-line.

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DESCRIPTION OF FIGURES.

PLATE 9, FIG. 2. A triple record of electro-cardiographic, jugular, and radial tracings showing sinus arrhythmia in the presence of acute heart-block (delayed conduction, *P–R* 0·3–0·4 secs., and *a–c* $\frac{1}{5}$–$\frac{2}{5}$ sec. Ventricular rate, 62 (Case XXVII).

FIG. 6. Acute heart-block during acute rheumatism. *P–R* interval prolonged, dropped beats. At other times periods of 2 : 1 block were recorded (Case IV).

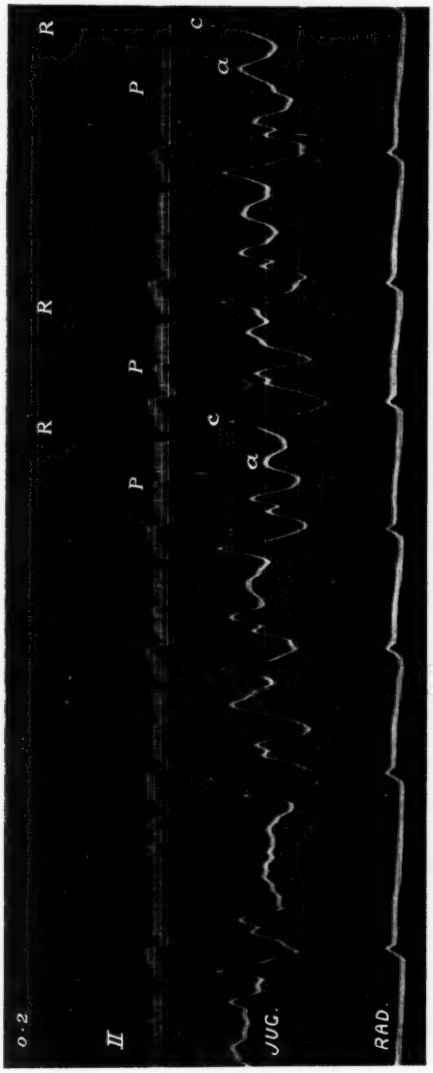

FIG. 2

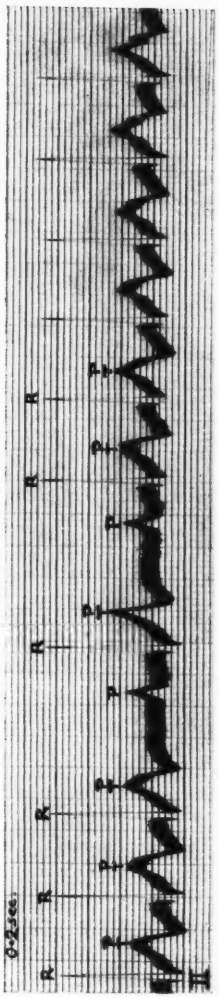

FIG. 6

STUDIES ON MALIGNANT MALARIA IN MACEDONIA

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I. *Introduction*

The Serbian Army, after landing at Salonika in the spring of 1916, suffered very severely from malaria. This disease is not widely prevalent in Serbia itself, so that the Serbian Army was to a very great extent exposed to it for the first time. The Serbs began to be infected during the retreat in the autumn of 1915, and their stay near Salonika for the purpose of equipment and training in the summer of 1916 caused the disease to become widely spread among them. The 41st General Hospital, to which we were attached as pathologists from the summer of 1916 to the end of 1918, was formed to act as a base hospital to the Serbian Army and treated Serbs exclusively. The severity of the disease was due to the high percentage of cases of the malignant tertian type, and the virulent form which this type assumed; the benign tertian type, though more widely prevalent, was in our experience never fatal, and was always rapidly amenable to suitable treatment. This paper will deal with the malignant type only.

(a) *Seasonal prevalence.* The seasonal prevalence of malignant malaria was very clearly defined, beginning about the middle of July and lasting to the latter half of October: in the earlier period of the year, from April onwards, the only form met with by us was the benign tertian. The species of *Anopheles* prevalent in July and August were also found earlier in the year, and we are unaware of any suggestion that the mosquitoes that carry the benign and malignant forms of malaria can be in any way differentiated, so that the late appearance of the malignant form is difficult to explain.

(b) *Severity of the disease.* The work of the Serbian Army during the first two months after our arrival in 1916 was very arduous, as they were engaged in a campaign in a mountainous country many miles from their base at Salonika, and medical arrangements for the transport of sick and wounded were extremely difficult owing to the lack of roads. In these early days a large number of cases arrived after many days' journey in a very serious condition; patients, who began their journey from the front line suffering from an attack of malaria, often

reached the hospital comatose and pulseless. The excitement of the campaign also caused others to continue in the trenches, though suffering from severe malaria, until they were completely exhausted. During the first six months of the existence of the hospital eighteen deaths occurred due to malaria alone, and twelve due to malaria complicated by some other disease, out of a total of thirty-nine deaths on the medical side. In the following seasons of 1917 and 1918 the number of deaths from malaria was considerably reduced. Much better communications had been established, so that the medical service could be greatly improved. Cases, however, arose from time to time in which coma occurred when the patients were lying quietly in bed, and were under treatment in the hospital itself, so that we were able to study the onset of serious symptoms from the beginning.

II. *Investigations undertaken.*

Our attention was confined mainly to the most severe cases, which we were thus able to study in considerable detail. Frequent blood-films were taken and examined by methods to be described later, and were correlated with the clinical condition of the patient, and special arrangements were made to obtain films in fatal cases just before death. Thorough post-mortem examinations were made by us as soon as possible, and the various organs were studied both in section and by means of smears made before the organs were removed. The distribution of the parasite in the body at death could thus be correlated with its distribution in the peripheral blood, which was often examined for several days before death. The changes in the blood-picture were also studied in other cases, which did not end fatally, both before and after the onset of severe symptoms. It was found that certain changes in the peripheral blood were of the utmost value in giving warning of the approach of a dangerous alteration in the patients' condition, and thus allowing the timely application of energetic treatment.

1. *Classification.* The result of our observations has been to convince us that there are three distinct pathological processes by which malignant malaria causes death, and that they are all directly dependent upon the liberation of toxin by the malarial parasite either locally or generally, and on the degeneration of tissues which is the direct result of the action of the toxin. The degeneration is fatty, and affects primarily the endothelial walls of the blood-vessels, though other structures, such as the heart-muscle, are also affected to a greater or less degree.

The methods by which the parasite of malignant malaria causes death are three in number, and the terminal illness can be classified into one of three groups.

(1) The first group we will call the *'True Cerebral'*, in which the cause of death is principally an intense invasion of the brain by malarial parasites. The brain apparently assumes the function which is usually ascribed only to the spleen and the red bone marrow, and becomes a factory for the development of the

malignant parasite in all its forms. In consequence of this the terminal symptoms are essentially cerebral. This type is probably always fatal notwithstanding treatment.

(2) The second group is characterized by an intense proliferation of the malarial parasite throughout the blood-stream generally; the condition being in sharp contrast to that usually existing in malignant malaria, where the identification of the parasite in the peripheral blood is often a matter of considerable difficulty. This type may be called the '*Septicaemic type*'. In consequence of the rapid increase of parasites in the blood an intense toxaemia arises which affects all organs. Clinically this type is characterized by a rapidly increasing severity of the patients' condition and an accentuation of general symptoms, which finally culminate in death. This form is above all others amenable to early and energetic treatment.

(3) The pathology of the third group centres round the heart; it may therefore be called the '*Cardiac type*'. As a result of repeated attacks of malignant malaria, assisted in most cases by fatigue and exposure, the heart-muscle fails and death finally follows. These patients may linger on for some considerable time with a scarcely perceptible pulse, but no other marked symptoms are usually observed.

Groups II and III tend to present pathologically many features in common, and in all probability in Group III an exacerbation of malarial infection is the determining cause of death; that is to say, a certain degree of increase of the parasites in the blood will be found just before death. On the other hand, in Group II the condition of the heart-muscle is always exceedingly striking, the terminal septicaemia causing very distinct pathological changes in it. The clinical picture of the two types is, however, very different. There are also intermediate forms between types II and III in which a distinct septicaemic condition arises with a very rapid and large increase of parasites in the peripheral blood, and quickly terminates a case whose heart, though much enfeebled, would not of itself have caused death.

2. *Methods.* Material for histological investigations was fixed either in a solution of 10 per cent. formalin in Müller's fluid for forty-eight hours and then transferred to plain Müller's solution, or in 10 per cent. formalin in normal saline solution. The tissue was then embedded in gelatine by the method described by one of us,[1] and cut on a freezing microtome. The stains used were Mayer's acid haemalum combined with either eosin or Sudan III. Fatty changes could thus be studied in detail, and it was found that parasites, even in the form of very fine rings, could be easily identified, being clearly stained by the haemalum.

Blood-films were examined after staining with Leishman's stain, and parasite counts were made by counting the number of parasites found against red corpuscles. With a little practice it was found that the number of red corpuscles in any particular field could be estimated with considerable accuracy, and the

[1] *Journal of Path. & Bact.*, 1912, xvii. 58.

number of parasites in the field could be counted: the number per cubic millimetre could be calculated either by making a count of the patient's red corpuscles, or by estimating these according to the anaemia present, which was found in practice to be sufficiently accurate. In addition differential counts were made of the types of parasite present. The leucocytes of the blood were also examined, and differential leucocyte counts were made.

III. Group I. *The 'True Cerebral Type'.*

1. *Details of a fatal case.*

Case I.—Serb. 1,242, aged 32, was admitted to hospital on October 11, 1916, suffering from a shrapnel wound of the right forearm. The wound progressed favourably, and his general condition was otherwise normal until December 28, when he became feverish, and on the following day had an attack of diarrhoea with abdominal pain. He passed mucus for two days, but then improved. On January 3, 1917, a further acute attack of diarrhoea occurred and the patient began to pass blood and mucus. He was therefore transferred to the Infectious Division. His condition was then as follows:

The pulse was small and fast, the tongue dry and white, and there was considerable tenderness over the abdomen, especially over the region of the sigmoid. The spleen was not palpable, but the liver extended well below the costal margin. His temperature was 101° F. He complained chiefly of pains in the head, legs, and abdomen. A history was given of four previous attacks of malaria. He continued to pass blood and mucus on the following day, but by January 6 the diarrhoea had stopped. On January 5, two days after the acute onset, he vomited once, but this did not occur again. On this day the headache was occipital and severe.

At 4 p.m. on January 6, he became suddenly comatose, and by 6 p.m. he could only just be roused. There were definite signs of lesion of the upper motor neurons on both sides; voluntary movements in response to pain were still present in both lower limbs. The temperature was then 104° F. and the pulse 140 per minute. The breathing was shallow and rapid. At 10 p.m. the coma had deepened, and the breathing had become of the Cheyne-Stokes type. He also vomited once. On the morning of the 7th there was only the very faintest response to the pain of intramuscular injection. There was, however, no rigidity. The left knee-jerk was increased, and the plantar reflex now gave an extensor reaction on both sides. Ankle clonus was also present on both sides. The pupils were large, equal, and sluggish, but there was still reaction to light. The temperature had come down to 101°, and the breathing continued rapid and was sometimes Cheyne-Stokes in character. Occasionally hiccough was present. The patient died at 12.5 a.m. on January 8, never having regained consciousness.

A blood smear was examined four hours before death while the patient was in a comatose condition. A fair number of fine rings were found, and in addition mature crescents, both male and female forms being identified. A quantitative count was attempted on this film about one year after it had been made in order to compare with counts from other types. Though the film was considerably faded, parasites could still be made out. The patient was very anaemic, and the total red count was estimated at 3,000,000 cells per c.mm., being the average of a series of actual counts on other patients with a similar degree of malarial anaemia.

The results were as follows:

Rings = 6,300 per c.mm.
Crescents = 200 „ „

the total count, therefore, was 6,500 per c.mm. This count, although it is just above the danger limit discussed later in the summary of Group II, is very low when compared with terminal counts to be given in the other types, and does not indicate any proliferation in the peripheral blood-stream.

Autopsy. 10½ hours after death.

Brain. There was considerable congestion over the cortex, especially on the vertex. On section, the white matter of the corona radiata and internal capsule was spotted over with deep red points, from which blood oozed, and which were of varying size (Fig. 1). They could not be removed by scraping with the knife. They were most conspicuous in the corona radiata, though also perfectly definite in the internal capsule. Similar spots, in small numbers, were also present in the caudate and lenticular nuclei. The region of the pons and medulla was free from these spots. The substance of the internal capsule was not uniformly white, but showed certain pearly-grey areas of small size which were frequently in relationship with one of the red spots, and corresponded with the necrotic areas about to

FIG. 1. The brain of Case II, showing the punctiform haemorrhages associated with the 'True Cerebral' type. The haemorrhages are shown as black dots surrounded by grey areas of necrosis. They are scattered throughout the white matter, but are especially numerous in the internal capsule. None are to be found in the grey matter. ⅔ natural size.

be described in the microscopic examination. The grey matter of the cortex did not show any sign of these red spots or any areas of degeneration. Small portions of some of the vessels in the spots were removed, and on microscopic examination no thrombosis or embolism could be demonstrated. Rings and crescents were present in the lumen in fairly large numbers.

Microscopically, the most striking feature of every section made was the presence of haemorrhages. These were numerous and varied in shape from oval to round. They measured 250 μ to 350 μ in diameter, and in some there was a central patch of fairly well staining brain tissue with an arteriole in the middle. These haemorrhages were always present in the white matter and never in the grey. The brain substance was torn up by them, and crescents and rings were identified in them (Fig. 2). In all the smaller vessels and capillaries free pigment was found in varying amount both in the brain and meninges. The polymorphonuclear leucocytes in the lumen were conspicuous because of the number of pigment granules in their protoplasm. The endothelial lining cells also contained granules of pigment here and there. In addition fatty degeneration of these cells was present. They contained fat globules of varying size and showed degeneration of their nuclei (Fig. 3). In the perivascular lymphatics of many of the smaller arteries pigment granules were to be seen, and the lymphatics themselves were distended with deeply staining lymphocytes in many places.

In the grey matter, all over the sections an increase in the lymphocytes was noted, especially aggregated round the nerve cells. The latter showed fatty particles distributed irregularly throughout their substance, which was more marked in some than in others. This fat was not concentrated in the oval pigmented area in which fat is normally present in adult nerve cells, and therefore is proof of a definite degeneration. The neuroglia cells were increased in number.

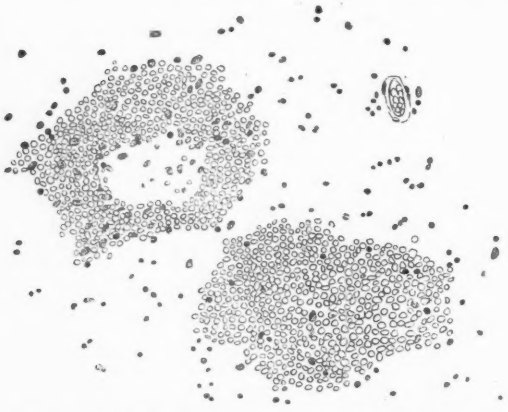

FIG. 2. Two haemorrhages in the white matter from Case II. They are roughly oval in shape and have ploughed up the fibres of the white matter. The upper one shows a central area in which no red corpuscles are present, but which contains a number of cells of the neuroglial type with oval nuclei. Some of these nuclei are irregular and degenerate, and the general structure in this central region is ill defined. On the right is shown a small blood-vessel. There is a general increase of lymphocytes throughout the white matter, their nuclei are shown darker than the larger and paler nuclei of the neuroglia cells. For the sake of clearness the ground tissue has been omitted. Zeiss, Ocular 4, Objective $\frac{2}{3}$. Reduced $\frac{2}{3}$.

FIG. 3. A small vessel in the grey matter of the brain showing fatty change, from a case of the true cerebral type. The endothelial cells contain globules of fat of varying size represented in the figure by black dots. In the lumen a polymorphonuclear leucocyte is shown at its upper end containing fat globules; five red corpuscles are also present, three of which contain parasites. Lymphocytes with dark nuclei are seen in the perivascular lymphatics. Zeiss, Ocular 2, Objective $\frac{1}{12}$. Reduced $\frac{2}{3}$.

In the white matter the most striking appearance, after the haemorrhages, was the presence of well-marked necrotic areas varying in size and shape. These were present in every section of the internal capsule. In some sections the capsule seemed almost entirely necrotic, the only healthy tissue consisting of small bands of various shapes and sizes running through the necrosed mass. In the centre of a necrosed area the whole of the brain substance had become so changed as to have no characteristics, but was simply an indefinable mass with no cells or nuclei to be seen. Outwards, towards the periphery, nuclei were seen staining faintly, and showing signs of disintegration; a gradual improvement could be traced till at the periphery comparatively normal tissue and healthy nuclei were reached. There was an increase in the neuroglia cells in the white matter, and lymphocytes too were more numerous. The medullated nerve fibres showed, in many places, signs of distinct nodulation and were undergoing degeneration. The forms of parasite found were the ring form or trophozoite, the crescent, male and female, and certain other transitional forms which will be described later. The number of parasites was very great in the capillaries of both white and grey matter. In some capillaries almost every blood cell contained a ring, in others scarcely one was to be seen, while in others again an intermediate condition was observed. Rings were most numerous in the capillaries of the grey matter, while the crescents had a preponderance in those of the white matter. In the meningeal and larger vessels the number of parasites was not nearly so great

as in the capillaries of the brain itself. No evidence of either embolism or thrombosis, in which parasites were involved, could be found in any capillary. Three blood smears were made from the brain, being taken from the red points from which blood oozed. In all three rings were found to be numerous, ranging from the thin fine ring to the larger and coarser ring forms. Mature crescents, male and female, were easily identified. Immature forms of crescent and transitional forms between ring and crescent were also found. The complete evolution of the crescent from the ring form was worked out from these specimens, and will be dealt with in a later part of this paper.

The enumeration of the parasites in these smears gave the following results, the red blood count being estimated at 3,000,000 per c.mm.:

Rings = 16,600 per c.mm.
Crescents = 500 „ „
Total parasites = 17,100 per c.mm.

This count is nearly three times as great as that of the ante-mortem smear.

Spleen. The spleen was very much enlarged, weighing 25 oz. The surface was smooth, and the cut surface was dark chocolate in colour, its substance was soft and pultaceous. On microscopical examination the Malpighian bodies and trabeculae were seen to be wider apart than usual owing to increase of the pulp tissue lying between them. In the Malpighian bodies the central arteries were distended with blood, and often a pale area was seen in which the nuclei stained faintly. This area had no fixed relationship to the central artery, and was not present in all. The faintly staining nuclei in it belonged to all the types of cell found in a normal Malpighian body, supporting cells, endothelial cells, and lymphocytes being involved, and also polymorphonuclear leucocytes. The protoplasm of these cells showed a well-marked fatty degeneration. The rest of the Malpighian body contained the usual large number of well-staining lymphocytes; but pigmentation and fatty degeneration were present to a slight degree in the endothelial cells and large supporting cells, and more conspicuously in the polymorphonuclear leucocytes. Few parasites could be found.

The pulp was very much increased, and was greatly distended with blood, though the increase was also partly due to pulp cells. Degenerative changes were found in the supporting cells, the pulp cells, the lymphocytes, and the polymorphonuclear leucocytes, The greatest degenerative changes were in those cells which contained the greatest amount of pigment, which was present in considerable quantity, either in single granules, or aggregated into small masses. The smaller clear pulp cells with deeply staining circular nuclei contained no pigment: the lymphocytes also contained none, and none was found free in the venous spaces. The polymorphonuclear leucocytes and the supporting cells contained pigment in varying amounts. The number of parasites was very large. They were present in all stages from the ring in its various phases, through the transitional and immature forms of crescent, up to the mature crescent, male and female; forms between ring and rosette were not identified. These crescentic forms were most plentiful in the venous spaces in the pulp and in the veins leading from them to the splenic vein. The ring forms were occasionally free in the pulp, not being enclosed in red cells. An enumeration of the parasites in the spleen smear was attempted, the red blood count being again taken as 3,000,000 per c.mm. The following is the result:

Rings = 21,000 per c.mm.
Crescents { mature male = 1,200; mature female = 600; immature = 1,800; transitional = 2,700 }
Total parasites = 27,300 per c.mm.

Filled-in ring forms were also definitely identified in the tissue of the trabeculae, lying in the interstices of the fibrous tissue, and not in lymph spaces or capillaries (Fig. 6). This is a possible position for the parasite to lie up in during the quiescent periods of the disease. The form found was always the filled-in ring, which was not enclosed in any cell.

Heart 12½ oz. The pericardial surface was normal. There was no dilatation, and the valves were normal in size and shape. The heart-muscle was fairly firm and of good colour. On section the wall of the left ventricle showed microscopically considerable distension of blood-vessels, in the lumen of which polymorphonuclear leucocytes containing pigment granules in varying amounts could be seen, almost all showing marked signs of fatty degeneration. Pigment floating free was seen in single granules, or in small aggregations. The endothelial lining cells of the capillaries contained a granule or two of pigment occasionally, and these cells also showed signs of degenerative changes in the form of globules of fat. The connective tissue cells showed distinct fatty changes. The muscle fibres on the whole stained normally, with the exception that in almost every cell a greater or less amount of fatty change was present in the sarcoplasm round the nucleus. This fatty change took the form of globules of irregular size clustered especially thickly at the two poles of the nucleus. In some cells, where this degeneration was most marked, the nucleus stained more faintly. In all fibres the striae were conspicuous and regular, even in those in which the degeneration was most distinct. There was no sign of any general fatty degeneration in the contractile part of the fibre. Parasites were not very numerous, but rings could be identified in red blood corpuscles in the capillaries. An occasional crescent was also seen. A smear was taken from the blood of the muscle wall and stained. The number of parasites found could not compare with that of the brain and spleen. Rings were identified and an occasional crescent was seen, also one or two early rosette forms. The immature forms of crescent were not found. Polymorphonuclear leucocytes, with granules of pigment enclosed, were readily seen, as also were large cells containing pigment. These cells were peculiar. They were about twice the diameter of a red blood corpuscle, and had a pale pink protoplasm with a pale blue nucleus, and were conspicuous by the granules of pigment they contained. They were most probably degenerate endothelial cells which had become loose in the blood-stream.

An enumeration of the parasites from the smear of the heart-wall gave rings at 4,200 per c.mm. No crescents were observed during this count. This was the only film in which mature asexual parasites were found in this case.

The liver was very large, weighing 79 oz. The surface was smooth and dark slate-blue in colour. On section the cut edges did not evert, and the cut surface was also slate-blue. The substance was fairly firm. The gall-bladder was normal.

Microscopic appearances. A marked round-celled infiltration was present, following the distribution of Glisson's capsule, being most distinct where the capsule left the peritoneal surface to run into the substance of the organ. This infiltration never invaded the periphery of the lobules themselves, but was concentrated round the branches of the hepatic artery and portal vein. The round cells stained well and their nuclei stood out prominently. They showed no sign of degeneration, and the infiltration appeared to be of comparatively recent origin, no marked increase of fibrous tissue being present.

The blood-vessels in Glisson's capsule were not distended, and the lobular capillaries contained a comparatively small amount of blood; the hepatic veins also were not distended, but contained pigment in fair amount, either free or enclosed in polymorphonuclear leucocytes, which in many instances were heavily pigmented. The endothelial lining cells of the capillaries also contained pigment in small granules here and there, fatty degenerative changes could be seen in

them, and many of the nuclei stained faintly. The stellate cells of Kupffer, which lie in the interstices between the endothelial lining cells and the columns of liver cells themselves, were most conspicuous objects. They were large and distended, and were, in nearly every case, packed with pigment, usually in the form of large, irregular round particles. They showed very distinct degenerative changes, the nuclei often being inconspicuous or even absent, while the protoplasm contained fatty globules of various size packed in amongst the pigment granules. Some were in such a degenerate condition that they were only identified by the large aggregation of pigment and fat present in them, which still preserved the shape of the original cells. In the liver cells themselves evidences of degeneration were plainly marked. They were small throughout, and were powdered over with fine droplets of fat. This became more accentuated towards the centre of the lobule, and in the most degenerate cells round the central vein the fat content was very large, here frequently taking the form of globules of considerable size. The nuclei of these cells were also in various stages of disintegration, from those which stained faintly to those in which fragmentation or total disappearance had taken place. In the less degenerate peripheral region certain liver cells had exceptionally large and deeply staining nuclei, while other cells had two nuclei; the protoplasm of such cells was less degenerate than that of most of the cells surrounding them; they may represent an attempt at regeneration. No bile could be seen in the liver cells. The wide spaces between the rows of shrunken liver cells at the centre of the lobule were filled in the main by swollen and degenerate stellate cells and endothelial cells; the number of red blood corpuscles present here was usually comparatively small. The increased size of the liver and its colour was chiefly due to these swollen endothelial and stellate cells.

The number of parasites identified was extremely small; a few rings were seen here and there in red blood corpuscles in the capillaries, and occasionally a crescent could be made out in a capillary. Corroboration of the comparative scarcity of parasites was obtained from a smear from the freshly cut surface of the organ. This was stained in the usual way, but no parasites of any form were identified.

Kidneys. Right 5½ oz., left 6½ oz. The surface of the kidney was smooth, and the capsule stripped easily. The cut edges did not evert, and the cortex was not markedly swollen. In the cortex the blood-vessels and capillaries were all distended with blood. In the glomeruli very little change was to be noted. The endothelial lining cells of the glomerular capillaries showed a few signs of fatty degeneration here and there. These capillaries were distended with blood, in which polymorphonuclear leucocytes were prominent owing to the pigment they contained. Certain of the glomerular epithelial cells also contained a fair amount of pigment, and showed more distinct signs of degeneration. The cells of the first convoluted tubules were swollen, with their margins on the inner side very irregular. Many of their nuclei stained very faintly, while others had entirely disappeared. A degeneration was present which was apparently of a dual nature. The first, and by far the most distinct, form was characterized by the formation in the cells of highly refractile droplets of various size which did not react to the fat stain with Sudan III, but remained unstained, and gave an irregular appearance to the cell. The second was a true fatty degeneration; here and there very minute globules of fat, staining with Sudan III, were to be seen. In the second convoluted tubules, large masses of physiological fat, staining brilliantly with Sudan III, were to be seen. The cells themselves appeared healthy, and their nuclei stained deeply. The connective tissue cells between the tubules contained a certain amount of pigment. The large vessels at the junction of the cortex and medulla were distended with blood, and the capillaries of the medulla were dilated. Their endothelial lining cells showed some fatty degeneration, and pigment granules were to be seen in them occasionally and also in the connective tissue cells. The loops of Henle did not show any degenerative

changes and appeared normal. The collecting tubules appeared normal except that in some of them a round droplet or two of fat could be seen. This is probably a physiological condition and similar to that found in the second convoluted tubules. Parasites were very few in number. Rings were not identified. Crescents, mature and immature, were seen in the capillaries of the glomeruli, and also in the small vessels lying between the tubules.

The stomach was not dilated. The mucous surface was covered with small petechiae, especially dense at the cardiac end. On microscopical examination, the blood-vessels were very much congested. This was especially marked in the vessels of the mucosa. The haemorrhages present were very strictly limited to the mucosa, being bounded by the muscularis mucosae. They were seen nowhere else. They extended from the muscularis mucosae to the free surface, and varied in size and shape, but none covered an area broader than that of three tubular glands. The vessels running between the mucous layer and the muscularis mucosae were extremely congested, and in certain places haemorrhages apparently started from them. Pigment was observed in the haemorrhages. In the capillaries of the mucosa a fair amount of it was seen in the form of small granules, and it could be demonstrated in their endothelial lining cells. These lining cells showed signs of degenerative changes, as also did the connective tissue cells, many of which were distinctly degenerate and contained pigment aggregated into small masses. The perivascular lymphatics were laden with pigment. Many round-celled infiltrations were seen in the mucosa and muscularis mucosae. Many of these ran up between the ducts to the surface. The most outstanding appearance, however, was found in the oxyntic cells, which showed a very marked degree of fatty degeneration. Their nuclei were mostly degenerate, staining faintly and undergoing disintegration, and the fat content of such cells was very large. The condition of the oxyntic cells was in marked contrast to that of the pepsin-secreting cells, whose nuclei were always well formed and stained normally, and whose protoplasm contained no fat. Slight fatty changes could be made out in the unstriped muscle cells of the muscularis mucosae. Parasites were not numerous, but a ring could be seen here and there in a red blood corpuscle either in a capillary or in a haemorrhage. An occasional crescent, mature or immature, was to be found in similar situations.

The distribution of parasites in the various organs showed that the only one which approached the spleen in parasite content was the brain. The numbers present in the heart were not greater than in the peripheral blood-stream before death, and other organs certainly contained still fewer. The peripheral blood-count shortly before death is one not uncommonly found in cases whose condition is not grave. There is thus no evidence of a great general increase of parasites throughout the body. This conclusion is also supported by the almost complete absence of the more mature asexual forms in either films or sections.

2. *Other fatal cases.* We have been able to examine, partially or completely, four cases in all who have died from malaria of this type, which is fortunately comparatively rare. Three of the cases occurred in our own hospital, and one, Case IV, we were able to examine through the kindness of the Scottish Women's Hospital, Ostrovo. Cases I and II have been worked out as completely as possible. Cases III and IV were not so completely examined, though all the essential points were substantiated.

In all four cases the onset was extremely sudden. In Case I, described above, it occurred in a man who was being treated for entirely different conditions, first gunshot wound, and later dysentery. The second and third cases

were admitted as malaria, but were not considered severe until coma suddenly occurred. The fourth case was admitted in a condition of coma. The duration of the severe condition, from onset to death, was never more than three days. The coma was intense to start with, and gradually deepened till death supervened. In each of our three cases the nervous symptoms distinctly pointed to a definite lesion of the upper motor neurons, rather than to a general cerebral irritation. A deepening flaccid paralysis occurred in Cases I and III, while in Case II, in the earlier stages, distinct rigidity was noticed on the left side. The breathing, at first always rapid, and sometimes stertorous, became gradually shallower, and often took on, towards the end, the Cheyne-Stokes rhythm, thus demonstrating the cerebral origin of the respiratory changes.

The heart did not show changes at the onset of the acute condition at all comparable to the rapid alterations in the nervous system. The pulse, though becoming in some cases very rapid, remained strong and regular; a condition in marked contrast to that in the cardiac type, in which the pulse is so feeble that it is often not felt at the wrist. The temperature charts showed nothing characteristic in any case.

In all four cases the punctiform haemorrhages in the white matter of the brain were conspicuous, but the relative number of haemorrhages in the internal capsule and corona radiata varied in different cases. In Case I, already described, and Case III, they were at least as numerous in a given area of the corona radiata as of the internal capsule. In the other two cases, on the contrary, the haemorrhages were extremely thickly scattered in the internal capsule, the number here being greatly in excess of that in a similar area of corona. This is of interest, as in Case II an early rigidity was present at the periphery, whereas in Cases I and III it was not noted. The notes of Case IV were not sufficiently full to enable us to give a definite statement concerning the presence of such rigidity. The haemorrhages in Case I were not absolutely confined to the white matter only. A small number were also present in the basal ganglia. This was, however, the only case in which haemorrhages were identified anywhere but in white matter. In no case were any haemorrhages seen in the pons or medulla. The microscopical appearances were in all similar to those described in Case I, the main variation being the extent of the areas of necrosis in the internal capsule, which varied with the intensity of the haemorrhagic change, and appeared to be dependent on this. The distribution of parasites was very similar in all cases, the crescents preponderating in the white matter and the ring forms in the grey, where, in Case III, one or two rosettes were also identified. The ring forms, in the grey matter especially, did not all appear to be enclosed in red blood corpuscles, but some were free in the lumen of the capillaries. We could not, however, convince ourselves that any form of capillary thrombosis was present in any case, either in the grey matter where the ring forms preponderated, or in the white matter in connexion with the haemorrhages. It would appear probable that, if the presence of large numbers of parasites either free or in red cells caused thrombosis and consequent haemorrhage and necrosis, this change ought to occur in the grey matter where the parasites preponderated. On the contrary, all haemorrhages and areas of necrosis, with the exception of those in the basal ganglia in Case I, occurred in the white matter, and had relationship to arterioles rather than capillaries. No sign of such changes was ever found in the grey matter. The actual numbers of parasites were estimated in Cases I and II by means of smears taken from the blood of the white matter at the post-mortem, and the counts gave remarkably similar results, the only difference being that crescents and forms intermediate between ring and crescent were more numerous in Case II than in Case I. The two counts compare as follows, the numbers given being those per c.mm. of blood with an estimated red blood count of 3,000,000 per c.mm.:

TABLE I.

	Case I.	Case II.
Rings	16,600	13,600
Crescents	500	1,200
Immature forms of crescent		5,700
Total	17,100	20,500

The condition of the spleen in the first three cases was similar, being in all extremely soft and almost pultaceous in consistency; the respective weights were 25, 17, and 17 oz. The Malpighian bodies of Cases I and II showed the fatty degenerate areas already described. These areas were not obvious in Case III, but here the number of lymphocytes were small, being replaced by a large number of larger cells with irregular nuclei. Parasites were present in large numbers in every case, crescents being extremely numerous and obvious. In both Cases I and II filled-in ring forms were definitely identified in the tissue of the trabeculae.

The condition of the heart in Cases I and II was very similar. There was, however, some dilatation of the right heart in Case II. This dilatation was still more marked in Case III. The blood-vessels were somewhat distended in all, but the fatty change and pigmentation of the endothelial cells of the arterioles and capillaries was slight compared to that in the brain. The condition of the muscle fibres in Cases I and II was practically identical. There was, however, some round-celled infiltration in Case II. The fatty change in these two cases was entirely confined to the sarcoplasm, and did not affect the general contractile tissue, whose striation was very well preserved. In Case III, however, a certain amount of degeneration of the contractile substance was also present in irregularly scattered groups of fibres. This was shown by a few fine droplets of fat scattered throughout the cell in addition to the larger droplets present in the sarcoplasm, and by indistinctness or complete absence of striation. Certain fibres also showed definite fragmentation, the rupture taking place along the line of striation, and the space between the separated ragged ends being filled in by débris or loose areolar tissue. This condition of fragmentation will be dealt with at greater length in the next type of case.

The number of parasites present in all cases was very few compared with their distribution in spleen and brain. Besides scanty numbers of ring forms a very occasional crescent was also seen in the larger vessels.

The liver in all three cases was again similar, weighing in each over 70 oz., and showing the slate-blue colour which is characteristic of malaria. The second and third cases differed from the first in that the organ was very soft and friable. This was apparently due in the second case to a considerably larger amount of blood in the capillaries at the centre of the lobule; while in the third case it was due to an extensive necrosis of the inner portions of the organ. In all cases parasites were scanty, though crescents and rings were identified.

The condition of the kidney in the three cases was in considerable contrast to that of the organs already described, for, with the exception of cloudy swelling in the cortex, little alteration from the normal was present. The cloudy swelling was not of great degree in Cases I or II. In Case III the necrosis, which has already been described in the liver, also involved the first convoluted tubules of the kidney. Many of these were completely degenerate so that cellular outline was lost and no nuclei could be seen. This degeneration spread into the medulla down the medullary rays. Parasites were few in each case. Crescents were identified in the glomeruli and in the vessels between the tubules, but ring forms, though seen, were very scanty and difficult to demonstrate.

The stomach of Case II was not examined. That of Case III did not show any of the haemorrhages so conspicuous in Case I, but the oxyntic cells were again conspicuous for their fat content. This was the more remarkable, as the

whole of the mucous membrane was very degenerate, so that the nuclei of the cells practically did not stain. This fatty change may either be ascribed to the malarial toxin, or possibly to the administration of quinine.

3. *Summary of Group I.* From the foregoing descriptions, the organ most markedly affected in this type is clearly the brain. The pathological condition found is thus in agreement with the clinical course which leads to death. The haemorrhages in the white matter were most certainly recent, and their occurrence would satisfactorily coincide with the sudden onset of coma, and give the anatomical reason for the paralysis, which is the chief clinical sign of the condition. The coma, again, is of the severe deepening type which is associated with definite cerebral lesions rather than with general cerebral irritation. The two pictures, clinical and pathological, therefore coincide. The condition of the brain is in marked contrast to that of the heart both clinically and pathologically. The amount of change in the latter organ found *post mortem* was, in the first two cases, comparatively slight. In Case III more severe changes were present, but these may be looked upon as a mild degree of the changes shortly to be described in the other two types. Clinically, in all three, the small amount of change in the condition of the heart was in great contrast to the rapidly increasing cerebral condition.

The number of crescents present in the spleen in all cases, and the great enlargement of that organ, lead to the conclusion that all were suffering from a chronic malignant malaria of long standing; and the wide distribution of crescents in the other organs examined and in the blood before death confirms this view; the widespread pigmentation present also supports this. The very large number of crescents present in the brain shows that this organ was deeply involved in the condition.

Towards the end of this paper a description will be given of the evolution of the crescent from the ring form, which has been worked out entirely in a smear from the brain blood of Case II. The complete cycle could be demonstrated. It is, therefore, reasonable to suppose that the evolution of the crescent was taking place in the brain. The usual situations in which such an evolution is held to take place are the spleen and the red bone marrow; but in these cases the number of parasites found in all stages of evolution supports the view that the brain also has become involved as a factory for the formation of the mature forms. Such a local increase of parasites gives rise to an excessive formation of toxin in the brain, and culminates by causing marked degeneration both of the endothelial lining cells of the small blood-vessels and capillaries and of the nerve cells themselves.

The degeneration of the blood-vessel wall becomes so severe that a critical stage is reached when a large number of vessels simultaneously give way, and give rise to the numerous and widely-spread punctiform haemorrhages characteristic of the type. The reason why the haemorrhages are practically confined to the white matter may lie in the fact that the structure of the vessels here is more primitive than that of the vessels of the grey matter. The blood supply of

the white matter is derived from the small vessels which pass through the perforating spaces at the base of the brain, and which are practically non-branching vessels of a very primitive type. The supply of the grey cortical matter, on the other hand, is from the highly developed meningeal vessels. The more primitive thin-walled vessel gives way before the more highly developed one, a fact which is fully recognized in the explanation of the common site of cerebral haemorrhage in or around the internal capsule. The presence of a few haemorrhages in the basal ganglia in Case I lends additional support to this theory, for these ganglia are also supplied with blood by the primitive perforating arteries.

To sum up, the view is here advanced that in this type of case the brain takes on the function usually associated only with the spleen and bone marrow, and becomes a factory for the manufacture of malarial parasites, especially the sexual forms. This leads to a condition of local cerebral toxaemia, which finally gives rise to definite cerebral lesions in the shape of punctiform haemorrhages throughout the white matter. These haemorrhages are clinically shown by the sudden occurrence of coma accompanied by definite signs of paralysis. The coma rapidly deepens, so that the patient cannot be roused, and the condition terminates in death within two or three days. When the condition is once established it is very doubtful whether any remedial measures can be of any avail. Our cases did not show the slightest response to energetic measures of treatment, and were in this respect the greatest contrast to cases of the other two types. The parasite count in the peripheral blood both during the severe illness and just before death does not correspond with the severity of the patients' condition, but remains low; it corresponds with the scanty distribution found in all internal organs excepting the brain and spleen. The scarcity of the more mature forms of the asexual parasite, taken in conjunction with these low counts, shows that no general rapid proliferation of parasites takes place.

IV. Group II. *The 'Septicaemic' Type.*

The second, 'septicaemic', group of cases has an entirely different clinical and pathological picture, the outstanding feature being the extremely high parasitic content of the blood both towards the end of the illness and also in all organs after death. The spleen is no longer the main place of storage and source of supply of parasites, but these are also found in very large numbers both in the free circulation, and in every organ of the body. This condition may arise not only in cases of chronic malignant malaria but also in cases of quite recent infection, and it appears possible that a very recent primary infection may thus rapidly lead to death. We have no direct evidence of this, for, in all the cases which terminated fatally, the great enlargement of both spleen and liver made it almost certain that the patients had had previous malarial attacks. On the other hand, the changes in the blood of two cases occurring amongst our own personnel approximated to those found in the fatal cases. These two patients were, as far as evidence could be obtained, suffering from

their first attack of malignant malaria. They were both dangerously ill, and it is possible that both would have died but for the energetic therapeutic measures taken.

A case of this type will now be described, in which no direct evidence could be obtained, in the shape of crescents either in the blood or in the organs, that the patient was suffering from chronic malaria. No history of a previous attack was given, but such evidence in the case of Serbs was of comparatively little value owing to language and other difficulties. The size of the spleen and liver, however, can be considered to negative the view that this was the patient's first malarial attack. It is, of course, possible that the enlargement of these organs was due to previous attacks of benign tertian malaria rather than of the malignant form, for mixed infections were not uncommon in Macedonia. Such a supposition would explain the absence of the crescentic forms of parasite. In all the other fatal cases in this group crescents were identified, though in some only in scanty numbers.

1. *Details of a fatal case.*

Case V. Serb. 5,880, age unknown, but certainly quite a young man, was taken off his ordinary duties on July 16, 1917, complaining of pain in the abdomen. He stayed quiet for three days, but on July 19, at 8.30 a.m., feeling worse he walked to the hospital, a distance of three miles. He then complained of general malaise and pain in the lower part of the abdomen and was also found to be suffering from a mild degree of bronchitis. There was no tenderness over the splenic area and the heart's action was good. He was constipated and was given a purge, and quinine by the mouth. He then walked the three miles back to his camp. About 1 p.m. he suddenly became unable to speak, staggered, lay down and appeared to have lost consciousness. His condition improved during the afternoon. He recovered consciousness, and about 5 p.m. walked about a little.

About 8 p.m. of the same day he again became unconscious quite suddenly and was brought up in a semi-comatose state and admitted to hospital at 10 p.m. His temperature was then 100° F., and he reacted to painful stimuli only though his reflexes were unaltered. His spleen was palpable and the heart's action was normal. 1½ grm. of quinine were given subcutaneously and repeated on the following day. That afternoon, July 20, he became very much worse; his temperature rose to 105·8° and his pulse to 160, though it was still fairly full and strong. His breathing was stertorous, the respiration rate being 44. A further dose of subcutaneous quinine was given. At 8 p.m. the patient died.

During life three blood-films were taken. A, at 10 p.m. on July 19; B, at 12.30 p.m. on July 20; and C, at 4.30 p.m. of the same day, the last being therefore taken within four hours of death. The striking feature of these films was the extremely rapid increase of parasites. The numbers per c.mm. were calculated on an estimated red count of 4,000,000, as the patient was not markedly anaemic, and are given in the following table:

TABLE II.

	A 10 p.m. 19.7.71.	B 12.30 p.m. 20.7.17.	C 4.30 p.m. 20.7.17.
Rings	3,000	8,000	91,400
Intermediate forms between ring and rosette or 'priors'	2,400	2,200	3,600
Immature rosettes	0	800	200
Mature rosettes	0	800	200
Total parasites	5,400	11,800	95,400

The great increase is thus seen to occur in ring forms, which in slide C were so numerous that four or five could be seen in every field. The other striking feature of these films was the presence of the mature rosette form of the malignant parasite and the forms intermediate between this and the ring form.

2. *Asexual forms of the malignant parasite.* We have made use of the term 'prior' for parasites which are intermediate between the ring form and the mature parasite, which has not yet assumed the rosette form; this latter we have called the immature rosette. The more advanced forms of the malignant parasite are easily distinguishable from the similar stages of the benign tertian parasite. The size of the corpuscle in which they lie is always small, and they never fill the whole of the corpuscle, even in the mature rosette stage never occupying more than two-thirds of the corpuscle. The 'priors' do not show the irregular amoeboid forms so characteristic of the benign tertian parasite, but are compact, round, or irregularly oval bodies still reminiscent of the filled-in ring, of which they are the further development. Their nucleus remains compact and undivided till indications of rosette formation are plainly visible, and the pigment which forms in them is aggregated at a very early stage into a single dense brown-black mass usually central in position. This is in striking contrast to the extremely scattered pigment of the corresponding stage of the benign parasite. The mature rosette is also markedly different from that of the benign form, in its small size, its relatively few segments, and its very compact dense black central mass of pigment. We have found such forms only in cases of malignant malaria which were in an extremely grave condition, and we consider that their presence in the peripheral blood is of great significance and a danger-signal of the utmost importance.

Autopsy, twelve hours after death, Case V.

Brain. The meninges were found to be congested, the congestion being of a much greater degree than that found in the cases of type I. Definite small meningeal haemorrhages were also present over certain areas: the largest of these was not more than ½ inch across. On cutting into the brain the vessels were found to be congested throughout, and certain minute haemorrhages were to be seen in the white matter in the region of its junction with the grey matter. These haemorrhages could be differentiated from the congested vessels, as their bright red colour could not be removed by scraping with a knife. They did not extend down the corona radiata, and none were to be found in the internal capsule. The vessels in the choroid plexus and in the walls of the third and fourth ventricles were also congested, but no obvious haemorrhage was to be found there. The whole brain was very soft, flattening out on the table when removed from the skull.

The small haemorrhages were readily substantiated on microscopical examination. Their numbers were very few in comparison with those of the previous type and their nature was different. The vessels generally were greatly congested in both white and grey matter, and round some of the comparatively large arterioles an irregular leakage of blood of small extent had taken place. Such haemorrhages were not only much smaller than those of type I, but were very irregular and, in the main, closely confined to the immediate perivascular tissue, the surrounding nerve tissue being scarcely involved. They were confined to the

region where the larger vessels run, namely, the junction of grey with white matter, and none were to be found in the main mass of the white matter itself. These scanty haemorrhages were thus in marked contrast to those in type I, in their size, shape, and distribution, and were not of such a nature as to cause any appreciable destruction of the nervous tissue of the brain itself. The endothelial lining cells of the arterioles and capillaries contained a certain amount of fine pigment and also showed minute globules of fat in the protoplasm of many of them. The amount of both fat and pigment was, however, small. Pigment was also identified free in the lumen of the vessels and polymorphonuclear leucocytes were conspicuously pigmented. Certain large cells were also found free in the lumen of the small vessels and capillaries, with much protoplasm and a round nucleus; they frequently contained a considerable amount of pigment. These are probably cast-off degenerate endothelial cells, which had become free in the blood. In addition to the fat in the endothelial lining cells dense masses of fat were also present, which were lying in the perivascular lymphatics. This fat sometimes partially outlined a small vessel in a most conspicuous manner. The number of lymphocytes in the perivascular spaces of the vessels was not very great. The whole of the grey matter was infiltrated with an abnormal number of round cells, which, to a large extent, had the appearance of lymphocytes. These cells were sometimes clustered round a capillary vessel in very considerable numbers and often were grouped round a nerve cell. The nerve cells themselves were in a condition of degeneration. In some the nucleus was markedly eccentric, stained badly, and no nucleolus could be seen, and the protoplasm of the cell was covered over with globules of fat spread diffusely throughout the cell. In others, the nucleus had completely disappeared, and the cell was represented only by a degenerate mass densely peppered over with fat globules. In the white matter also there was a marked increase of round cells distributed diffusely. They were not so conspicuously grouped round the capillaries as they were in the grey matter, but lay in groups between the medullated fibres. The latter showed distinct evidence of degeneration, being irregularly nodular and tortuous in course. No evidence of localized necrosis was to be found. Parasites were most extraordinarily numerous both in the grey and in the white matter. They were present in all forms from the ring to the mature rosette, but no crescents of any kind were ever found. The number of rings in certain capillaries of the grey matter was enormous. They were not only present in every corpuscle in the capillary, but were also lying extra-corpuscularly free in the lumen. In other capillaries similar numbers were present, but the stage of the parasite was more advanced, as was shown by the presence of distinct aggregations of pigment in each parasite. The mature rosette stage was also quite frequently met with, scattered among the other forms. Most of the capillaries contained red cells, the majority or the whole of which contained parasites. Some capillaries, however, were still to be found in which no parasites were to be seen. The capillaries in the white matter contained vast numbers of parasites, though their numbers were less than in the grey. Parasites could also be seen in quantity in the larger vessels, though here their identification was always more difficult. They were present in numbers and in every stage in the small haemorrhages lying at the junction of the white with the grey matter. An estimate of the numbers present was attempted by a count of a smear taken at the post-mortem from the blood oozing from the cut surface of the brain. The count obtained was 128,000 parasites per c.mm., or more than six parasites to one field. This count exceeds the ante-mortem count taken less than four hours before death.

The *spleen* was very much enlarged, weighing 25 oz. Its surface was smooth. On section the substance was of a deep chocolate colour. It was soft and fairly friable, but could not be considered in any degree pultaceous. Microscopical sections showed that the whole of the organ was greatly distended

with blood; the large blood-vessels were engorged throughout and the pulp was packed with red cells, and was greatly increased in amount relatively to the Malpighian bodies, which were thus widely separated.

In the Malpighian bodies lymphocytes were diminished in number and the supporting cells correspondingly increased. The large branched supporting cells were very conspicuous owing to their pigment content. Occasionally a few globules of fat were also present in those cells which were most highly pigmented, and the nuclei of such cells were degenerate, being irregular and staining feebly. The only other cells to show any pigmentation or fatty degeneration were the endothelial lining cells of the capillaries and the polymorphonuclear leucocytes present in the vessels themselves, but the amount of degenerative change was slight. The cells present in greatest quantity, which replaced lymphocytes, were not the supporting cells already described, but round or oval cells with clear protoplasm and a very conspicuous nucleus with very bright chromatin network. These cells showed no fatty change and contained only the scantiest traces of pigment. The areas of degeneration, which have been described in cases of type I, were not found. Certain of the branched cells contained malarial parasites, usually in the ring form, as many as three or four sometimes being present in one cell. The number of parasites, however, was comparatively small in the Malpighian bodies, as no red corpuscles were present to contain them.

The pulp was most conspicuous for its extreme distension with red corpuscles. Pigment was also present in large quantity. The largest masses of this pigment were contained in the large branched supporting cells, many of which were in various stages of degeneration; their nuclei frequently stained very feebly, and in some the nucleus was completely absent; others, still further degenerate, could only be identified by the characteristic shape of their very great pigment content. The cells of this type also contained a little fat, but this was never present in large quantity. Many of them contained parasites usually in the ring form, such parasites being present in the more degenerate of these cells: as many as four or five could often be seen in a single cell. The comparatively small cells with clear protoplasm and bright nuclear chromatin showed little change, occasionally a granule or two of pigment being present in them. Other cells, with a clear round cell body of considerable size and an oval faintly staining nucleus, frequently contained pigment and cells of other types such as red corpuscles and the smaller cells described above. They also often contained parasites, but not in such large numbers as the branched supporting cells. Pigment, besides being present in the cells described, was also found free in a finely divided state. Parasites were excessively numerous throughout the pulp; most were contained in red corpuscles, but a certain number, usually in the form of filled-in rings, were identified lying free. They were present in every stage from the small ring form up to the mature rosette, very large numbers of 'priors' with characteristic masses of pigment in them being observed. Rosettes also were numerous and easily identified. Notwithstanding the very large number of parasites, not a single crescent, mature or immature, could be found.

Certain areas of the pulp contained an extremely dense aggregation of ring parasites. In these areas all cells were undergoing degeneration; their nuclei stained faintly and often were fragmenting or had almost completely disappeared. Parasites in the form of filled-in rings were also definitely identified lying in the fibrous tissue of the trabeculae of the spleen, their situation having no relationship to any blood-vessel or capillary. The identification of the parasite in this situation has already been described in the cerebral type; its importance will be discussed later, when considering the possible places where the parasite may lie up in cases of chronic relapsing malaria.

The *heart* was normal in weight, weighing 12 oz. It was, however, greatly dilated in all its cavities, and its substance was extremely soft, so that the whole heart flattened out when removed from the body and laid on a flat surface. The

dilatation was of such a degree that four fingers could be passed through the tricuspid valve and three fingers through the mitral. The valves were otherwise normal. The heart-muscle was very pale, soft, and easily ruptured by the pressure of a finger. Microscopical examination showed all the large vessels, both arteries and veins, in a state of extreme congestion, but no evidence of thrombosis could be found. In certain areas the capillaries also shared in this extreme congestion; in others they were not so conspicuous, though even here they were abnormally distended. Some large pigmented cells were frequently seen in the lumen with rounded nuclei which were apparently cast-off endothelial cells. Polymorphonuclear leucocytes were conspicuous for their pigment content. Finely granular pigment was also seen lying free in the vessels and capillaries. and in the endothelial lining cells of the small arteries and capillaries. The latter also showed fatty degeneration to a mild degree. The number of lymphocytes was not increased and no round-celled infiltration was seen. The muscle fibres

FIG. 4. The heart-muscle of Case V, showing the fragmentation of muscle fibres found in the 'Septicaemic' type. Fragmentation takes place along the line of the cross striation and occasionally, as at *a*, a segment between two striae is completely separated. Striation is still well preserved, but general fatty change, represented in the figure by black dots, is present both in the form of larger globules in the sarcoplasm round the nucleus, and in fine droplets scattered through the contractile fibres. Capillaries are shown lying between the muscle fibres. Zeiss, Ocular 4, Objective $\frac{1}{6}$. Reduced $\frac{2}{3}$.

(Fig. 4) were most markedly fragmented throughout, the change being similar to that described in Case III, type I, but much more extensive. The fractured ends were often quite widely separated from each other. Notwithstanding this the striation of the contractile substance was still extremely conspicuous in all fibres throughout the section, whether such fibres showed only slight fragmentation or fragmentation of the highest degree. The rupture in the fibres always took place along the line of the striae. The nuclei of the fibres, whether much fragmented or not, all stained well and did not appear to be degenerate. The cell bodies, however, showed throughout a most marked fatty degeneration; not only was the sarcoplasm round the nucleus filled with conspicuous globules of fat of various sizes, but the whole of the contractile substance was powdered over with fine globules of fat. This condition was not uniform, but was universally present to some degree. Certain areas, usually those in which the fragmentation was most marked, showed the change to a very high degree. The coincidence of

such marked fatty change with a still well-preserved striation was a remarkable feature of the sections. Parasites were extremely numerous in all vessels, being both intra-corpuscular and extra-corpuscular. In the capillaries the distribution varied. Most contained very large numbers, and in some every corpuscle contained a parasite; other capillaries could, however, be found in which the numbers were comparatively few. The parasites were present in all stages from the ring form to the mature rosette. The ring forms predominated, but all stages were common. Free parasites were also found lying in the lymph spaces between the muscle fibres, and by careful searching others could be identified lying in the sarcoplasm of the muscle fibres themselves (Fig. 5). In this identification

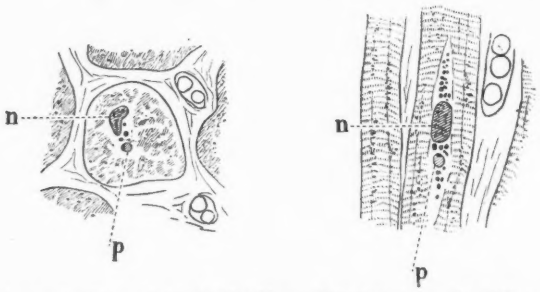

FIG. 5. Showing parasites, *p*, lying in the fibres of the heart-muscle of Case VI. The muscle fibre is shown in transverse section on the left, and the parasite is seen lying in the sarcoplasm in the same plane as the nucleus, *n*, and globules of fat. Capillaries containing red corpuscles are also shown. The same is seen on the right in longitudinal section. Fatty change in the fibres is extensive. Zeiss, Ocular 2, Objective $\frac{1}{12}$. Reduced $\frac{2}{3}$.

great care was taken to eliminate the presence of a fine capillary crossing the fibre, in which the parasite might really be lying. Observations were made on sections 5 μ thick, and the presence of fat globules in the sarcoplasm, lying close against the parasite and in the same focal plane, assisted in its definite localization. The matter was finally decided by the definite identification of parasites in parts of the sections, in which the muscle fibres were cut at right angles to their long axis, so that the parasite was obtained lying in the central sarcoplasm and completely surrounded by the contractile substance of the particular fibre. The form in which such parasites were found, whether lying in the muscle itself or in the lymph spaces between the muscle fibres, was always the filled-in ring, identical with the form already described as having been found in the trabeculae of the spleen. Though repeatedly searched for, no crescents, either mature or immature, could be discovered in any section.

The *liver* was greatly enlarged and weighed 79 oz. Its surface was smooth except for a small amount of old perihepatitis over the diaphragmatic area. On section it showed a surface uniformly slate-grey in colour. Its substance was softer than normal. Microscopically, in Glisson's capsule there was a general increase of round cells, but the cellular increase was nowhere of the intensity found in the cerebral type. There was no great congestion of vessels in the capsule, but the congestion at the centre of the lobules was most marked. The liver cells throughout were greatly shrunken and degenerate, and the cell columns were widely separated from each other, especially at the centre of the lobule. Many of these had nuclei, which stained faintly or not at all, and protoplasm which was densely infiltrated with droplets of fat of small size. Towards the periphery of the lobule the cells were better preserved, but none of them were free from signs of degeneration in the shape of fine droplets of fat and a shrunken protoplasm. The liver cell columns were throughout separated by rows of deeply pigmented large stellate cells. At the centre of the lobule the separation was accentuated by the marked back pressure congestion, but nearer the periphery it

was entirely due to these large swollen cells, which were always highly pigmented. The endothelial lining cells of the capillaries were also swollen, pigmented, and fatty, and assisted in this separation. The stellate cells varied greatly in size. Some were extremely large, being bigger than the adjoining liver cells, and having a large oval nucleus. Others were very highly pigmented and showed every grade of degeneration, their nuclei being very feebly stained and irregular or entirely absent. Some of these cells also showed their degeneration by the presence of droplets of fat, but on the whole this was not a very marked feature. Some of the large stellate cells appeared to have become detached and to be free in the capillaries. In addition small round cells were present between the liver cell columns, which were lymphocytes or young proliferating stellate cells. Bile was practically absent. Parasites were easily found, but were not so numerous as in other organs. All forms from the ring to the mature rosette were present, and certain of the ring forms did not appear to lie within cells, but to be free in the capillaries. A few parasites in the ring form were identified here and there within the body of degenerate stellate cells. Though carefully searched for, no crescentic forms could be found.

The *kidneys* were practically normal in size, weighing 5 oz. each. Small haemorrhages were present in the capsules of both, and were removed by stripping them. The surface that was left was smooth. On section, the cut edges slightly everted, but the cortex and medulla were normal in appearance. The pelvis showed small submucous haemorrhages similar in size to those in the capsule. On microscopical examination, the larger vessels were not markedly congested, but the capillaries, especially of the glomeruli, contained a fairly large amount of blood. The condition of the organ was otherwise similar to that of Case I. Parasites could easily be found, but were not so numerous as in organs such as the brain, heart, and spleen. They were present in all forms from the ring to the rosette, and could be easily seen both in the capillaries of the glomeruli and in the other capillaries of the organ. No crescents were seen.

A count was taken of the number of parasites in blood removed from the splenic vein at the post-mortem, in order to compare it with the count of blood from the inferior vena cava. It was considered that the splenic vein blood should give a much higher count than that of the inferior vena cava, if the great increase of parasites was due to an intensive production in the spleen; if, however, the condition was due to a general proliferation all over the body, the two counts should be similar. The numbers found were as follows: 27,000 per c.mm. in the blood from the splenic vein, and 24,000 per c.mm. in the blood from the inferior vena cava. The difference in these two counts is within the limit of error, and it may therefore be assumed that the number of parasites in the blood from the two sources was practically identical, that is to say, that the number of parasites supplied to the main circulation by the spleen was practically identical with the number supplied by the rest of the body. The spleen, though so crammed with parasites, was no longer one of their chief sources, but they were being produced in quite as great a proportion throughout the whole body. The number of parasites found in these two smears is, however, very markedly inferior to that in the smear taken from the peripheral circulation four hours before death. This number, 95,000 per c.mm., is again inferior to the count of the brain blood, namely 128,000 per c.mm. It is apparent, therefore, that an accumulation of parasites had taken place, both throughout the general peripheral capillary circulation and even more markedly in the capillary system of the brain. This may

possibly be due to a mechanical filtration, but we have seen no evidence to support the view that such a filtering takes place. It appears to us much more likely that this preponderance of parasites is due to actual rapid proliferation of them in these situations.

The striking feature of this case was the extreme rapidity of the course of the severe illness. The patient was ill only four days, and only on the third of these did he consider himself sufficiently ill to demand treatment. That is to say, the serious period of his illness was less than thirty-six hours. During this period he was given subcutaneously 4½ grm. of quinine, or approximately 70 grains, without any practical influence on the course of the disease.

The first blood-film, A, was taken before any quinine was given, and the parasite numbers were then over 5,000 per c.mm. The second film, B, was taken after 3 grm. had been given, and the count had not only not dropped, but had risen to approximately 12,000. The third film, C, showed a still further increase to nearly 100,000 per c.mm. It is quite clear, therefore, that the quinine administered had no effect in controlling the rapid increase of parasites.

Arguments have already been brought forward from the parasite counts of the various organs, that the condition was one in which a general rapid proliferation of the parasite was taking place throughout the whole body, that is to say, in the capillaries of all organs, especially the brain, and also in the peripheral subcutaneous capillaries. The condition had, therefore, become similar to that obtaining in benign tertian infection, with, however, this important difference, that it was apparently uncontrollable by quinine. Ordinarily, the number of parasites found in the peripheral stream in malignant tertian infection is comparatively small, the spleen and bone marrow being the only manufactories. In this case, however, the process had become universal, and if controllable by quinine at all, controllable only with extreme difficulty. As we take this view of the pathology of this group of cases, we have designated it the 'septicaemic group', meaning by that a true infection of the general blood-stream, so that proliferation takes place in it. The general condition of the organs can be ascribed to the intense toxaemia which the extensive parasitic infection had given rise to. The heart was conspicuously affected, its muscle showing a most acute fatty change. Nevertheless, the pulse remained fairly good almost till death. The cerebral symptoms were those rather of irritation than of gross lesion. Coma was never profound and unconsciousness was intermittent. This is in contrast to the deep coma with signs of definite lesion which occurs in cases of the cerebral type.

3. *Other fatal cases.*

Case VI. A second case of a similar intense and rapidly fatal general infection by the malignant parasite occurred in Serb. 2,122 T, who had been under treatment for six weeks for dysentery. At the same time he was taking 10 grains of quinine orally every evening, as he was obviously also suffering from malarial cachexia. Suddenly, at 8 p.m. on November 4, 1917,

he became very ill, and within one hour's time he was semiconscious with a temperature of 103° F., and a rapid, full, and bounding pulse. He was also very restless. Malaria was suspected, and he was immediately given 20 grains of quinine intramuscularly. On the morning of the 5th he was more comatose, but could still be roused. He was then given a further dose of 15 grains of quinine intravenously. No physical signs of any definite cerebal lesion were found. He rapidly got worse, and died at 2 p.m., eighteen hours after the acute onset.

In this case again the treatment, though more energetic, was begun too late, and was quite powerless to control the rapid proliferation of the parasite and consequent death from toxaemia. A count was made of a blood-film, taken when the patient was *in articulo mortis*, and showed the extremely large total of over 270,000 parasites per c.mm. of blood; 'priors' were also present. An examination of blood-films taken earlier would have revealed the imminence of the condition, so that earlier and even more energetic measures of treatment could have been adopted with a good chance of success.

The question of the existence of chronic malaria in this second case was not in doubt. Not only was the condition of malarial cachexia present, but also examination of smears showed the presence of crescents in all organs. The enlargement of the liver and spleen was also great, the former weighing 86 oz. and the latter 28 oz., and their pigmentation was intense.

The organs, both macroscopically and microscopically, were strikingly similar to those in Case V. There was the same degeneration of brain with an even more intense parasitic infection, the count of a brain smear giving 450,000 parasites per c.mm. as against 128,000. The heart, again, was dilated, and extremely soft. Its muscle fibres were peppered all over with fine droplets of fat, and fragmentation of fibres was present, though not in the extreme degree of the first case. Parasites were very numerous, a count giving 140,000 per c.mm. Parasites were again definitely identified free in the lymph spaces and also in the sarcoplasm of the muscle fibres. The liver and kidneys were practically identical in both cases. The spleen was slightly larger, weighing 28½ oz. It was very soft and the cut surface was almost pultaceous; microscopically, the whole pulp stained poorly, so that the identification of the finer ring forms of parasite was very difficult. The Malpighian bodies contained a greater number of lymphocytes than in Case V. All forms of parasite were identified.

The spleen substance gave a parasite count of 120,000 parasites per c.mm., the splenic vein a count of 240,000. The count of 270,000 from the peripheral blood in life was bigger than these; this therefore supports the conclusion that active proliferation was taking place throughout the general blood-stream. The brain smear gave by far the largest count, just as in the previous case. The count from the heart is practically equal to that from the spleen smear, being about one-half that of the peripheral blood just before death, and may be taken as indicating the count of any internal organ with the exception of the brain.

The condition of the organs found in these two cases and in others of the septicaemic group was thus mainly an acute degeneration especially affecting the brain, heart, spleen, and liver.

Degenerative changes in the endothelial cells of the blood-vessels, though very definitely present, were less conspicuous than in the cerebral type; although in certain regions, such as the meninges of the brain and the capsule of the kidney, definite haemorrhages had taken place. The diffuse degenerative changes in the organs were not, however, due to circulatory disturbance, but to an intense general toxaemia.

The virulence of the toxin of the malignant parasite, when liberated into the general circulation by the rupture of the rosette, is demonstrated by a case, Case VII,

who came into our hospital at too late a stage for successful treatment, although his condition was recognized directly after admission, and the most energetic measures were taken.

Case VII. The patient, Serb. 10,107, was admitted on the evening of August 14, 1918, in a condition of almost complete unconsciousness. A blood-film taken at 6.30 p.m. (Table III) gave a count of 32,000 parasites per c.mm., nearly all the parasites being in an early 'prior' state, that is, completely filled-in rings of large size: a few very fine rings could also be found. After three intravenous injections of 15 grains of quinine the patient's general condition greatly improved, and the number of parasites in the peripheral blood diminished considerably to 11,000 only. A later film showed a still further diminution of the more mature forms, which now showed rosette formation, and a great increase of the earliest ring forms; his temperature had then risen to 103·2° F., and thus corresponded with the appearance of the fine ring forms of a fresh cycle. The quinine given had therefore diminished the developing parasites of the earlier cycle in the peripheral circulation from about 30,000 to 3,000, but had not prevented the beginning of a new cycle. That evening the patient had considerably improved, but at 7.30 p.m. he suddenly died; the physician, though immediately sent for, was not able to arrive before death had taken place.

TABLE III. *Parasite counts of Serb. 10,107.*

	Rings.	Priors.	Immature Rosettes.	Mature Rosettes.	Total.
In Life					
6.30 p.m., 14.8.18	very few	mostly	0	0	32,000
10 a.m., 15.8.18	very few	0	mostly	0	10,800
5 p.m., 15.8.18	16,400	400	0	2,800	19,600
P.M.					
Inferior vena cava	20,300	—	—	900	21,200
Blood from cavity of left ventricule	27,200	800	—	21,200	49,200
Splenic vein	4,000	—	—	14,400	18,400
Spleen juice	67,400	—	337,100	943,800	1,348,300
Liver juice	16,000	2,000	2,000	22,400	42,400
Kidney juice	8,000	—	—	10,000	18,000
Brain juice	69,600	800	1,600	118,400	190,400
Brain blood	63,200	—	—	13,600	76,800

At autopsy the condition of the organs was similar to that described in Case V. An extensive series of smears were taken, and all showed (Table III) that by far the greater number of parasites were in the mature rosette stage, either ready to burst or having actually ruptured in the process of making the smear. No crescents were found, and forms between the ring and rosette were exceedingly scanty. The number of fine rings was fairly large in certain situations.

The sudden death of the patient therefore coincided with the arrival at the mature rosette form and subsequent rupture of a very large number of malignant parasites, and the conclusion is justifiable that the liberation of toxin, the early indication of which was given by a rise in temperature, soon became so rapid and great as to cause immediate death. Such an almost simultaneous rupture of malignant rosettes is luckily extremely rare, for it seldom happens that practically all the parasites are in the same phase. In the benign tertian form, on the other hand, such an occurrence is common, and the liberation of the toxin causes the

typical malarial attack. The difference of virulence of the toxin liberated by the two types of parasite must be very great.

4. *The action of quinine on the distribution of parasites.* As certain deductions can be drawn from this case concerning the action of intravenous quinine on the distribution of parasites in the body, the details of various counts are shown in Table III.

It will be seen from the count of the inferior vena cava blood that the number of parasites in the circulation is very similar to that found at the periphery just before death. In the blood of the left ventricle, after it had passed through the lungs, a considerable increase of parasites was found, especially of rosettes; these had presumably been washed out of the lung tissue by the circulating blood. The number of parasites present in the spleen was enormous, and consisted to a very great extent of mature organisms, mostly ready to rupture. The actual number of organisms supplied to the general circulation through the splenic vein was however surprisingly small, though in contrast to the inferior vena cava blood, mature rosettes predominated.

In the liver the number of rings was similar to that in the general circulation, but large numbers of mature parasites were also present. In the kidney, though the number of rosettes was considerable, the total count was not large. The brain showed a very large number of both rings and rosettes, but the number of mature parasites was very much smaller than in the spleen. The count of the brain blood was a somewhat doubtful value as it was to some extent contaminated with brain juice; it however showed a great decrease of mature forms in comparison with the latter. From these counts it is evident that the numbers of mature parasites in the general circulation were very much less than in the organs themselves. Taking this in conjunction with the counts in life the administration of intravenous quinine had certainly diminished the parasites free in the circulation. It is difficult, however, to imagine that quinine had affected the parasites in such organs as the spleen and brain, in which the numbers present were still enormous. We may conclude that the chief immediate action of quinine is upon parasites free in the circulation, rather than upon all parasites in the body. It may, however, also have an effect in diminishing the output from the organs into the general circulation, for the number of parasites present in the splenic vein was very low, when we consider the immense numbers present in the spleen itself. The output of mature parasites from the brain was also small compared to the large numbers present in the organ. Intramuscular quinine, probably owing to its slower absorption, does not produce this rapid diminution of output. This is shown in Cases VI and XI, in which the splenic vein count was about double that of the spleen juice.

It is probable that a fatal termination can only be brought about in this septicaemic type by the diffuse liberation of toxin throughout the body, and that so long as the asexual cycle is confined to organs such as the spleen, the toxic dose is not sufficient to cause death. The immediate effect of quinine is upon the parasites in the general circulation. If the invasion of the general blood-

stream is discovered at a sufficiently early stage, it can be controlled by energetic administration of quinine and the fatal termination can be prevented. In illustration of this we will now give an account of two cases occurring amongst the hospital personnel, in which the detection of the presence of rosette and prior forms in the peripheral blood led us to fear a fatal issue, but in which treatment was successful in bringing about recovery.

5. *Cases of recovery.*

Case VIII. Private R. had been in Macedonia in our unit just over a year. It is possible that a previous primary attack of malaria may have been masked by prophylactic quinine; but he had never had any severe malarial attack. He was well in health until the evening of October 13, 1917, when he had various indefinite abdominal symptoms. On the morning of the 22nd his temperature was 99° F. On the morning of the 24th he was admitted to hospital with a temperature of 105° F. His spleen was not palpable. A blood-film taken at

TABLE IV. *Private R.*

	10.30 a.m. 24.10.18.	6 p.m. 24.10.18.	9 a.m. 25.10.18.
Rings	4,800	9,200	12,400
Priors	1,200	800	2,800
Rosettes	200	0	0
Total	6,200	10,000	15,200

10.30 a.m. on that day, Table IV, gave a count of 6,200 parasites per c.mm. In this film a mature malignant rosette was definitely identified and several prior forms were also seen. As the extreme importance of the appearance of this form of parasite in the peripheral blood was not then realized, the immediate intravenous administration of quinine was not insisted upon, but further films were taken. A second count from a film taken at 6 p.m. and examined next day gave a total of 10,000 parasites per c.mm. The rapid increase of parasites showed that quinine ought to be administered without delay, and an intramuscular injection of 20 grains was given at 9.30 a.m. Another film then taken gave a total of 15,200 parasites per c.mm. This latter count is larger than the count taken in Case V eight hours before death: the rate of parasitic increase was almost identical in the two cases. On the afternoon of the 25th the patient's condition suddenly became very serious. At 2 p.m. he was given food, which he easily swallowed, and he could talk normally. At 4 p.m. he was able to swallow only with great difficulty, and his speech had become very indistinct and guttural; at 5 p.m. 15 grains of quinine were given intravenously. At 6 p.m. he could just be roused: breathing was stertorous and hiccough was frequent. He had incontinence of urine. His pulse was good. On the following morning his condition had improved, though his pulse was slightly weaker. He was given a further 15 grains of quinine intravenously. He was that evening also given 20 grains of quinine intramuscularly. On the 27th improvement was maintained, and two similar doses of intramuscular quinine were given. The temperature became normal. This treatment was continued on the 28th. The following day intramuscular quinine was discontinued, and 20 grains were given by mouth, three times a day. The patient then appeared to be out of danger, but the heart sounds were weaker than they had been, and the pulse was small and soft though regular. The spleen could not be felt. From this date onwards improvement was continuous and no further rise of temperature took place.

Comparing this case of recovery with the fatal ones already detailed, the suddenness of onset of the serious condition was again conspicuous. At 2 p.m. on the 25th no dangerous symptoms were present; while at 4 p.m. they were extremely marked. The patient had been under continuous observation from the 21st, and the results of the examination of the films of the morning and evening of the 24th, the day before the onset of serious symptoms, were taken as an indication that most urgent measures of treatment were necessary. An intramuscular injection of quinine was therefore given, and it was determined that this should be followed by an intravenous injection directly any more serious symptoms appeared. The reaction to the intravenous dose was marked, and the patient had improved considerably in the twelve hours following its administration. A further intravenous injection again caused improvement, and in another twenty-four hours he was well on the way to recovery. We hold that this case would have terminated fatally in the same way as Cases V and VI but for the energetic treatment that was undertaken before serious symptoms arose. The effect of toxin on the heart appeared late, when the serious general symptoms had been recovered from. This supports the view that the cause of death in the septicaemic type is a general toxaemia, and is not primarily due to the poisoning of the heart-muscle only.

TABLE V. *Sister C.*

	10 a.m. 18.9.17.	6 p.m. 18.9.17.	10 a.m. 19.9.17.	9 a.m. 20.9.17.	1 p.m. 20.9.17.	6 p.m. 20.9.17.
Rings	0	0	0	0	1,200	2,000
Priors	0	0	0	one in half-hour	400	400
Immatures	0	0	0	0	400	0
Total	0	0	0	1	2,000	2,400

Case IX. Sister C. first reported sick on October 18, 1917, with a temperature of 104·8° F. The temperature remained up throughout the day, and blood-films taken were negative, Table V. The following day the temperature was normal at 6 p.m. A film was again negative. Next day her condition was worse, her temperature reaching 105° F. late that evening. In a morning film only one parasite in the form prior to the rosette was found in over half an hour's search. In the other films taken parasites were easily found. The patient was given 16 grains of quinine intramuscularly on the evening of October 20, owing to the form of parasite found in the blood, and a similar dose the following morning. The patient was then transferred to another hospital.

The subsequent history of this case was only vaguely known to us, but the malarial attack was very severe, and the course of illness very prolonged. We quote this case here, as it was peculiar in that the first parasite found was in the form prior to rosette, indicating that the attack would be extremely serious.

6. *The rate of disappearance of parasites under treatment with intravenous quinine.*

In neither of these cases with recovery were parasite counts continued after quinine had been given intravenously or intramuscularly, so that the rate of

disappearance of the parasites from the peripheral circulation was not studied. A final case, Case X, Serb. 9,446, which, but for treatment, would probably have developed the septicaemic form of the disease, illustrates the rate of disappearance. The counts are given in Table VI.

TABLE VI.

Date.	Temperature F.	Parasites.
12 noon 13.8.18	104·8°	11,600
9 p.m. 13.8.18	99·2°	19,000
6.30 p.m. 14.8.18	100·6°	6,000
9 a.m. 15.8.18	99·2°	1,600
6 p.m. 15.8.18	101·2°	2,000
9 a.m. 16.8.18	100°	—

Rings only were found throughout, but the counts on the first day showed that the peripheral infection was intense and was increasing. On the analogy of Private R., Case VIII, serious clinical symptoms were to be expected on the following day. Treatment by intravenous injection was begun directly the first count had been obtained, and its results were shown by the rapid fall in the number of parasites. From the third day after the first intravenous dose parasites could no longer be found in the blood. The patient never developed any dangerous symptoms, and his recovery was rapid. The disappearance of the malignant parasite from the peripheral circulation is therefore not so rapid as that of the benign, for which it is almost useless to search after quinine has been given; the malignant parasite, however, disappears in 2 or 3 days under suitable treatment.

7. *Summary of Group II.* The danger limit of the parasite count. From our present experience we hold that frequent examinations of blood-films in cases of malignant malaria of any marked severity give most important indications as regards the probable course of the disease and the necessary measures of treatment to be taken. The discovery of a comparatively high parasite count is an indication that the count should be watched and further films taken at frequent intervals. It must be remembered that the number of ring forms of the malignant parasite in the peripheral blood of a case in an acute attack varies considerably with the temperature; when the temperature is at its maximum they are extremely few, but when the temperature is at its minimum they are more frequent. A count in an ordinary case will seldom be found to reach 5,000 parasites per c.mm., or 1 parasite to every 4 fields of 200 red cells. If a higher count than this is found, the presence of a septicaemic condition should be suspected, and frequent counts should be made. The presence of rosette forms and the forms prior to these is

usually stated to occur in the peripheral blood only in fatal cases shortly before death. The two cases VIII and IX just quoted, however, show that such forms can be found in patients who are not at the moment dangerously ill. Their presence is nevertheless a danger signal of the utmost importance, which appears before the clinical condition has become grave. It is reasonable to consider that their presence in the peripheral blood proves that the proliferation of the parasite is no longer limited to the spleen and bone marrow, but that it is already taking place all over the body and that a rapid increase is beginning. The above arguments, of course, have no reference to the presence of the sexual crescentic forms in the peripheral blood, which may be extremely numerous, and should not be included in any count. It is quite possible that, if sufficient warning is obtained by early examination of films, quinine will always prevent a fatal termination in this type, and may even be so successful as to prevent the appearance of grave symptoms.

To sum up, the 'septicaemic' type is characterized by an intense and rapid proliferation of the asexual cycle of the malignant parasite throughout the body, which gives rise to an intense toxaemia affecting all organs and leading to death. The asexual cycle is usually confined to such organs as the spleen and bone marrow, and the toxin liberated by the rupture of the rosette only reaches the blood-stream comparatively slowly, and never becomes highly concentrated in it. When, however, the asexual cycle takes place in the general circulation, the virulence of the rapidly liberated and concentrated toxin is such as to cause grave general symptoms, which, if untreated, are rapidly followed by death. Treatment in an early stage is an entirely different matter to treatment when once severe symptoms have occurred.

The fatal cases of the septicaemic group, already described, did not show clinically marked symptoms of heart failure until just at the end. The toxic effects were chiefly shown by the cerebral symptoms. In Case VIII the pulse remained good throughout the period of intense cerebral disorder, and it was not until the fifth day after admission to hospital with a temperature of 105° F., and the fourth day after the onset of the cerebral symptoms, that the action of the heart became enfeebled. The effect of the acute toxaemia in this type, therefore, takes a few days to manifest its action on the heart-muscle, when the latter organ is in a healthy state at the beginning of the attack.

V. *Cases intermediate between Groups II and III.*

Many cases of chronic malaria, however, have an enfeebled heart owing both to the chronic toxaemia and the accompanying anaemia. In cases of this type the septicaemic condition may manifest itself clinically more by cardiac than by cerebral symptoms, and the patients may die of heart failure without any obvious cerebral changes.

We will now give the salient points of two fatal cases in which the septicaemic condition was very marked according to the evidence of blood-films both in

life and at autopsy, though the symptoms were not so acute in onset as in the cases already described. The parasite counts in one of these cases were even higher than those already given; that is to say, the general infection and proliferation were even more intense. These cases may be looked upon as intermediate between Groups II and III. In Group II, the 'septicaemic', the condition is one of an intense malignant malarial septicaemia in a patient with a comparatively healthy heart. In Group III, the 'cardiac', the dominating factor is a heart greatly enfeebled by chronic malaria, whose contractile power is finally destroyed by a small increase of malarial toxin produced by a comparatively slight terminal general infection. The two factors, the intensity of the malarial infection and the feebleness of the heart's action, are interdependent as regards production of a fatal termination. When the one is great, the other need only be slight, and vice versa. It follows that intermediate forms may occur in which both factors will play a comparatively important part; the heart, though enfeebled, will only succumb with the added effect of a fairly intense septicaemic condition.

Case XI. Serb. 6,378 was admitted on August 21, 1917, at 11.30 a.m. He was drowsy, and his pulse was feeble and of low tension. Later on in the day he became very restless, and his pulse became imperceptible at the wrist. He passed numerous stools during the course of the day. He was infused intravenously and subcutaneously with normal saline and was given stimulants; he was also given 20 grains of quinine intramuscularly. He rallied and went to sleep. That evening the pulse could not be felt at the wrist, but could be felt in the carotid artery, and had a rhythm of 136 per min. He was given two further intramuscular injections of 20 grains of quinine, but died of heart failure at 10.45 a.m., August 22.

A count made the day before death showed 540,000 parasites per c.mm.; rosettes, mature forms, and prior forms were all found in some numbers. This count was the largest we have ever obtained from a film of malignant malaria taken in life, and represents an average of 27 parasites in every field examined. It is clear therefore that, although the clinical picture in this case was in the main cardiac, an extremely intense septicaemia was at the same time present. This is borne out by the examination of the various organs.

The *brain* was congested, but no haemorrhages were present. There was a general round-celled increase throughout both white and grey matter, and all signs of degeneration were present in the nerve cells, though degeneration was not so marked as in Cases V and VI. There were marked collections of fat in perivascular lymphatics, but comparatively little fat or pigment was present in the endothelial cells of the arterioles and capillaries. Parasites were extremely numerous: the count from a smear gave the huge total of 730,000 per c.mm. Prior forms and rosettes were easily identified. After prolonged search two mature crescents were identified in the capillaries of the grey matter.

It is remarkable that with such an intense infection of the brain cerebral symptoms were not more conspicuous, for the concentration of toxin in the organ must have been very large.

The *spleen* weighed only 13 oz., and was not very soft. Microscopically, the Malpighian bodies were wide apart, and contained definite degenerate areas as in Case I. The pulp was increased and congested, but not to the extent found in Case V. There was a considerable increase of the medium-sized, clear, round pulp-cells with conspicuous chromatin in their nuclei. Supporting cells were often densely pigmented and markedly degenerate with conspicuous fatty change; occasionally a parasite could be identified inside a supporting cell. The number

of parasites was large, and they often occurred in groups; a count of a pulp smear gave a total of 360,000 per c.mm. Rosettes and priors were numerous, and in addition two crescents were definitely identified in the smear, proving the case to be chronic; these were not included in the count given above. Filled-in ring forms were definitely identified in the trabeculae, both lying in the lymph spaces and between the fibres of the elastic and fibrous tissues (Fig. 6). A parasite count was also made on a film of the splenic vein blood, and gave a total identical with that in the brain, 730,000 per c.mm. This count is practically double that of the spleen pulp, and therefore shows that parasites were being freely liberated from the spleen, the output not having been affected by the quinine given intramuscularly. This is in contrast to the inhibition of output under intravenous quinine in Case VII. It is impossible to say whether it is a bigger count than would have been obtained from the peripheral circulation just before death, but on the whole this is improbable as the peripheral count was already 540,000 the day before.

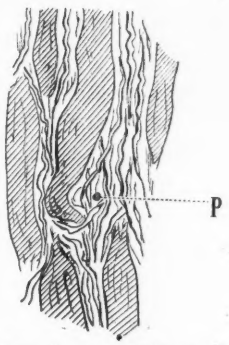

FIG. 6. A parasite, *p*, in one of the trabeculae of the spleen of Case XI. It is in the form of a filled-in ring, and lies free between the thick strands of fibrous tissue and the thin elastic fibres. Zeiss, Ocular 2, Objective $\frac{1}{12}$. Reduced $\frac{2}{3}$.

The *heart* was small, weighing only 8 oz., and was not greatly distended; the tricuspid valve admitting $3\frac{1}{2}$ fingers, the mitral two. The muscle was pale and abnormally friable, but the heart did not collapse on the table when removed from the body. Microscopically, there was considerable congestion of the heart wall, both veins and capillaries being distended. The muscle fibres showed fatty degeneration of marked degree, large globules of fat being present in the sarcoplasm round the nucleus, and finally divided particles being scattered throughout the contractile substance. Fragmentation could not be substantiated, but many fibres showed a marked loss of striation and their nuclei were degenerate. This condition varied from place to place, but was always most marked where fatty changes were also greatest. The number of parasites was large, a count of the heart-muscle juice giving a total of 525,000 per c.mm. Rosettes and priors were easily found, but no crescents were identified.

The heart in this case showed signs of a much more prolonged toxic effect than in Cases V and VI. The fibres were not ruptured, but their striation had become feeble in many places, and had even disappeared. Macroscopically, the organ was not so soft as in Case V, but its muscle was nevertheless pale and very friable. Its cavities were not markedly dilated.

A film was also taken of a small mesenteric haemorrhage which was present in the region of the ascending colon. A count from this gave a total of 290,000 parasites per c.mm.; both priors and rosettes were found. This haemorrhage may be looked upon as a toxic manifestation, being due to leakage through a damaged vessel wall.

The *liver* was not greatly enlarged, weighing only 62 oz. It was however intensely pigmented. The stellate cells were very large and the liver cells very degenerate, fatty, and shrunken; marked round-celled infiltration was present in Glisson's capsule. Parasites were not as numerous as in the other organs already described, and no crescents were found. A few ring forms were seen in the stellate cells.

The *kidney* showed little change, except for fairly conspicuous cloudy swelling in the first convoluted tubules.

Case XII. The second fatal case, Serb. 6261, had a definite history of chronic malaria for over ten months. He was admitted on August 16, 1917,

with a normal temperature and with his general condition good. He had then been ill four days. On the following day his temperature rose to 101° F.; he was therefore given 10 grains of quinine three times a day by the mouth. On the 19th he was not so well; he had had a restless night, and was dull and confused. His pulse was feeble and his lips were blanched, the pulse-rate being 140 at midday. He was given two intramuscular injections of 20 grains each during the day and a further injection on the following morning. He was also given stimulants. On the morning of the 20th his pulse improved a little, but during the day it got worse, then became imperceptible, and he finally died of heart failure at 5.40 p.m. A blood-film was taken on the 19th, thirty hours before death, and gave a count of 58,000 parasites per c.mm. A mature rosette and several priors were found in it. This count showed that a marked septicaemic condition was present in this case also: the clinical symptoms were distinctly those of heart failure.

The condition of the *brain* confirmed this, as nearly every red corpuscle in the capillaries of both grey and white matter contained parasites, and many rosettes were also found. The general condition of the organ was very similar to that in Case XI; the vessels were generally congested, but no haemorrhages were present; little pigment was to be seen, but fat was most conspicuous in the perivascular lymphatics. There was a general increase in round cells and the nerve cells were degenerate.

The *spleen* weighed 22 oz. Its substance was very soft, but microscopically the pulp did not appear to be excessively congested; pigmentation was marked throughout, having the usual distribution; fatty change was also well marked.

Certain portions of the pulp tissue were degenerate and stained badly and indefinitely; these areas were peppered all over with fat globules of small size. The identification of parasites was difficult, but considerable numbers were seen, mainly in the ring form. A few crescents were also identified.

The *heart* was greatly dilated, the tricuspid valve admitting five fingers, the mitral three. The heart-muscle was flabby, but of a good colour. Microscopically, fragmentation of fibres was marked, and in addition a diffuse fatty change was present, the fat lying not only in the sarcoplasm, but also finely scattered over the contractile substance. Striation was fairly well preserved throughout, but varied inversely with the amount of fatty change. Parasites were found both as rings and rosettes, but did not appear to be excessively numerous. This was, however, difficult to ascertain, as the ring forms found were very small and delicate, and therefore difficult to identify in section.

The *liver* weighed 72 oz. and was slate-grey in colour. Marked patches of round-celled infiltration were present in Glisson's capsule; the liver cells were shrunken and degenerate throughout, and widely separated by deeply pigmented stellate cells. The degeneration of the liver cells was not extreme, and their nuclei stained fairly well even at the centre of the lobule. The number of red blood corpuscles in the organ was not large, and parasites were again difficult to identify, but a fair number of fine rings were seen in the red corpuscles present.

The *kidney* showed cloudy swelling of the first convoluted tubules, and fatty changes and pigmentation in the endothelial walls of the glomeruli and intertubular capillaries. Parasites were identified in the form of very fine rings.

No history was obtained in Case XI, but the presence of crescents in the spleen renders it probable that the case was chronic. Case XII was clearly a case of chronic malaria, for crescents were identified in the spleen, and there was a definite history of malaria of nearly a year's duration. The spleen and liver were also both very greatly enlarged. The condition of the brain was practically identical in the two cases, but the heart of Case XII, in contrast to

that of Case XI, showed very marked dilatation. With this it also showed distinct fragmentation of muscle fibres similar to that in Cases V and VI, though not so extensive.

The two cases XI and XII may be looked upon as intermediate between the septicaemic and cardiac types. The evidence of blood-films showed them to be septicaemic; on the other hand, clinically their final condition was one of heart failure. At autopsy the heart of Case XI did not macroscopically obviously demonstrate a condition of heart failure, but that of Case XII was markedly dilated and flabby, and approximated to the condition found in the cardiac type, which is about to be described.

VI. Group III. *The 'Cardiac' Type.*

1. *The Serbian heart.* The number of Serbs that were admitted with apparently failing hearts into our hospital when we first began work was large. It has been claimed that there is something peculiar about the Serbian heart. It is always much smaller than that of an Englishman of corresponding size and weight, for the heart of an average Serb seldom weighs more than 9 oz. With this small heart the Serb has power of continuing to exist while apparently pulseless for a surprising period; for instance, in Case XI the whole of the day before death the pulse could only be felt in the carotid, not at the wrist. A large number of these failing hearts were in cases of malaria, and in our early days a considerable proportion of the deaths which took place were those of Serbs suffering from malignant malaria, who arrived in this pulseless condition. Unluckily our laboratory facilities were not at that period fully developed, and so this type of case has not been as fully investigated as we should have liked; but, nevertheless, a fatal termination in malaria, which clinically was apparently due to heart failure alone with no marked cerebral manifestations, forms a very definite type. This type we have called type III, and we will now give a description of a typical case. The organization of hospital accommodation and means of transport for the sick improved rapidly at the end of our first three months' existence as a hospital, so that we did not subsequently admit any patients in the condition of complete exhaustion frequently met with in early days. It can therefore be presumed that the cardiac type is only likely to be fatal when hospital arrangements have to cope with an overwhelming number of serious cases. Another factor was also present in the early days. The various hospital staffs were to a large extent without experience of malaria, and sufficiently energetic measures of treatment were not taken, because the extreme virulence of the malaria which occurs in Macedonia was not then recognized, and the severity of its action on the heart was not realized.

2. *Details of a fatal case.*

Case XIII. Serb. 872, aged 34, was admitted on September 22, 1916, with a history of malaria of ten days' duration.

He was in a state of collapse. Brandy was given and also 30 grains of quinine per day by the mouth. On admission his temperature was 103·6° F.; it

fell to normal next day, and was still down on the morning of the 24th. He was then in a state of collapse with cold extremities, and his pulse was not palpable at the wrist. The heart was not found to be enlarged; on auscultation a tic-tac rhythm was heard, the rate being 160 per minute. He was given an intramuscular injection of ten grains of quinine.

That evening his temperature was again over 103°. On the next day it was down in the morning, but rose in the afternoon, and he died at 7 p.m., September 25.

The *autopsy* took place fourteen hours later. As no cerebral symptoms had occurred the brain was not examined.

The *spleen* weighed 15½ oz. Its surface was smooth, but it was very soft and flabby. On section the substance was found to be pultaceous. Its colour was a dark blue chocolate. Microscopically, the Malpighian bodies were rather widely separated; but their appearance generally was fairly normal. The supporting cells and endothelial cells showed little change, though some contained a certain amount of rather finely granular pigment and small globules of fat. The capillaries themselves were not markedly distended, but certain of them were conspicuous by the number of parasites they contained, either free or in red cells, though the majority did not contain any. The pulp was increased, but not greatly congested except for the larger venous spaces. In certain areas red cells were very scanty; in some the tissues generally were degenerate. Pigment was mainly to be found in the branched connective tissue cells, and was specially concentrated in cells which were degenerate. It was also present in some quantity in large phagocytic cells with pale nuclei, which in addition often contained red corpuscles and occasionally malarial parasites. The smaller cells with clear protoplasm and round nuclei seldom contained pigment. The polymorphonuclear leucocytes present were frequently highly pigmented, and pigment was also present lying free in the blood spaces. Fatty change was very inconspicuous in any cell with the exception of a few globules in the polymorphonuclear leucocytes and in the branched supporting cells. The number of parasites present was fairly large, though not in any way comparable to type II in this respect. They tended to lie in groups, and though the majority were to be found within red corpuscles, a certain number were free. Ring forms preponderated, but crescents, both mature and immature, were identified in fair numbers. A few prior and rosette forms were definitely identified.

The *heart* weighed 10½ oz. and was very markedly dilated, especially on the right side. The tricuspid valve admitted five fingers and the mitral three. The valves themselves were otherwise normal. The heart-muscle was pale, flabby, and very soft. Under the microscope the arteries were not found to be distended. The capillaries were, however, full of blood over fairly large scattered areas. The smaller veins in connexion with these were also widely distended. Occasionally a small haemorrhage had taken place from such a vein. These distended veins contained an excess of polymorphonuclear leucocytes and lymphocytes, and also large numbers of parasites, the polymorphonuclear leucocytes containing a considerable amount of pigment and often being fatty. The endothelial cells of the capillaries and veins contained an occasional globule of fat or pigment, but no considerable quantity. No marked perivascular infiltration was present.

The muscle fibres showed fragmentation over considerable areas. This fragmentation was very definite, but was not so extensive or of such degree as in type II already described. The torn ends were not so widely separated, and the number of ruptures in any particular fibre was not so great. The striation of a very large number of the muscle fibres was either poorly marked or not to be seen. Certain fibres showed irregular patches of indefinite striation only, while in others no striation at all could be made out. This loss of striation was not universal, for in some areas very well defined striae could still be seen; it was, however, widely spread, and was on the whole most marked where frag-

mentation was most extensive. The amount of fat present in the muscle fibres was not very great. In most a fair number of globules of various sizes were to be seen in the sarcoplasm round the nucleus, but none were to be found over the contractile portion of the fibre. In those fibres where striation was lost, the contractile substance had a hazy, indefinite, finely granular appearance, but these fine granules did not colour with the fat stain. The nuclei of the more degenerate cells, which had lost their striae, were usually irregular, shrunken, and feebly staining. Occasionally fibres could be met with with two nuclei; these were usually of the better preserved type with striation. The greater number of parasites in the vessels were in the filled-in ring stage, or in the prior form with a marked eccentric collection of pigment. Rosettes were also identified, and early ring forms were numerous. No crescents were definitely identified. Certain of the filled-in ring forms were also found lying between the muscle fibres, presumably in lymph spaces, and others were definitely identified lying in the sarcoplasm of the muscle fibres.

The *liver* weighed 72 oz. Its surface was smooth. The cut surface was of a uniform bluish red colour. The cut edges everted, and the liver substance was very soft and friable. Microscopically, there was some general infiltration of Glisson's capsule with round cells. This infiltration did not involve the surface of the organ, but at those places where it was most marked tended to invade the periphery of the lobules. The liver cells were fairly well preserved throughout. Their columns were not so widely separated as in the types already described. The cells at the periphery of the lobule contained globules of normal fat and normal nuclei. At the centre of the lobule, however, fatty degeneration was present and the cell nuclei stained poorly. Even these degenerate cells at the centre of the lobule were, however, not much shrunken. The liver cell columns were separated by finely pigmented stellate cells and endothelial cells, which showed little fat and their nuclei stained well. In certain regions, the capillaries were considerably distended with red corpuscles, especially near the centre of the lobule and in the region just under the capsule of the organ. The large hepatic veins contained, besides red blood corpuscles, cast-off fatty liver cells and also pigmented stellate cells, both types lying free in the lumen mixed with blood cells. Parasites were found fairly extensively throughout the organ. Most were found within red corpuscles, but some appeared to be free in the capillary lumen, and occasionally one or two were found in the body of a stellate cell. The commonest forms of parasite were the filled-in ring and the early 'prior'. Plenty of smaller rings were also present, and a few rosettes were identified. Crescents, both mature and immature, were also found sparsely scattered throughout.

Kidneys. Each weighed 5½ oz. The capsule stripped easily, leaving a smooth surface. On section the cut edges everted, and the cortex appeared swollen and pale. Otherwise they were normal. Under the microscope, both arteries and veins were seen to be markedly distended; the capillaries in both cortex and medulla were also dilated to a variable degree. The glomeruli appeared to be normal except for pigmentation of certain of their cells, and the presence of an occasional parasite in the capillary lumen. The first convoluted tubules were markedly degenerate. In many regions the nuclei of their cells had completely disappeared, and the cell body was swollen and irregular, and contained granules and globules of various sizes which did not stain with Sudan III. In other regions the degeneration was not so marked. The cells of the second convoluted tubules appeared normal, though in certain tubules some of the lining cells had desquamated. In the medulla the capillary congestion was marked in certain areas, but the tubules appeared well preserved. The interstitial tissue was not increased either in cortex or medulla.

Parasites were present throughout the organ, scattered fairly sparsely both in the glomeruli and in the capillaries between the tubules. They were usually

intracorpuscular and in the form of the ring or the early 'prior'. No crescents were identified.

3. *Summary of Group III.* Unfortunately no films of the peripheral blood during life were examined, and no smears were made from the various organs at autopsy, so no direct comparison was possible with the parasite counts made in the cases of the other types, which occurred later and were more thoroughly investigated. As there were no cerebral symptoms in this case, it was not considered necessary, in the state of our knowledge at the time, to make a post-mortem examination of the brain; for in other cases of this group the examination of the brain had shown macroscopically nothing abnormal. We are therefore unable to compare the condition of the brain with that in the true cerebral and septicaemic types. As clinically the cerebral symptoms in these two types were in our experience always present and definite, it may be assumed that no changes of a comparable degree were present. The condition of the heart was the outstanding feature in the morbid anatomy of the case. Dilatation of the cavities was very marked, and the state of the myocardium was very degenerate. This degeneration was not so acute as in the cases of type II, for macroscopically the heart on removal from the body preserved its shape to some extent, while microscopically the striking feature was the loss of striation in the contractile portion of the muscle fibres, and a diffuse granular degeneration accompanying this, rather than an acute fatty degeneration. Clinically also, the cardiac failure was the striking feature. The patient was pulseless for some time before death, and the heart rhythm was rapid and running.

The condition of the liver also gave evidence of heart failure as, although the central veins were not markedly distended, considerable back pressure congestion was present in the capillaries of the majority of its lobules. Signs of back pressure were also present in the spleen, where the venous spaces were congested, while the arteries were not; and in the kidneys, where both arteries and veins were distended with blood. The distribution of the parasites was fairly uniform throughout the organs examined, with the exception that the number present in the heart was distinctly large in proportion. This is in contrast to the condition found in types I and II, where the heart count tended to be comparatively low. The number of crescents was not very large except in the spleen, where sufficient were present to justify the view that the case was one of chronic malaria. The number of forms of parasite between the ring and rosette, and the identification of definite rosette forms in all organs, showed that a general invasion of the blood and a general reproduction of the parasite in it had developed; that is to say, that a terminal septicaemia was present. The numbers present, however, did not in any way compare with the intensity of infection in cases of type II. The conclusion may therefore be drawn that the actual determining cause of death was a septicaemia of comparatively mild degree reacting on a heart already badly damaged both by previous malaria and by exhaustion.

From this and other cases of the cardiac group examined we have come to the conclusion that a terminal malarial septicaemia had always been present in

all cases that ended fatally with the clinical signs of heart failure. It is improbable that the condition of the heart itself, even in the most chronic forms of malaria, can lead directly to death.

This is an important point with regard to treatment, as it indicates that no condition of the heart in a case of chronic malaria can contra-indicate energetic treatment by quinine, if there is the slightest clinical indication that such a treatment should be pursued.

We have separated Cases XI and XII from the cardiac group, and considered them to be intermediate between this and the septicaemic group, because of the very high parasite counts obtained in them from the blood in life and from smears of the organs. Clinically, they both presented a terminal picture very like that in the cardiac type, of which Case XIII is an example; but they showed in addition to signs of a failing heart a certain degree of cerebral irritation, which took the form of restlessness and some lack of control of the sphincters. The only method available for comparing the intensity of the parasitic infection in the three cases was by comparison of the distribution in sections. The number of parasites present in the organs of Case XIII and other cases of the same type was certainly much less than in Cases XI and XII. The condition of the heart in the latter two cases was an intermediate one; fatty degeneration, which was so intense and conspicuous throughout the muscle fibres in Cases V and VI, was also present in them to a lesser degree, but was superimposed upon a condition of chronic degeneration, in which the striation of the muscle fibres was to a great extent lost, their protoplasm had undergone granular degeneration, and their nuclei had degenerated. This chronic degeneration was of the same nature as that present to a greater degree in Case XIII.

To sum up: the cardiac type is characterized by a chronic degeneration of the heart-muscle due to repeated attacks of malignant malaria, which finally leads to death from heart failure, owing to further poisoning of the degenerate muscle by a fresh malarial attack. Extraneous causes such as fatigue, which further weaken the heart's action, are important accessory factors in the final illness. The terminal malarial attack ends with a mild degree of that general invasion which in a much more pronounced form is the determining cause of death in the septicaemic type. If the cardiac exhaustion is recognized before it is extreme, and early warning of the septicaemic condition is obtained, the outlook in cases of this type is hopeful. The condition of the heart, however serious it may be, never contra-indicates the energetic administration of quinine, as a terminal septicaemic condition of greater or less degree is always the determining cause of death.

VII. *Summary of the Histological Changes in Malignant Malaria.*

The pathological changes in the various organs can all be ascribed to the effect of the toxin liberated by the malarial parasite, and the degeneration of tissues consequent upon this. The liberation of pigment also is a factor in causing changes in certain cells. The type of degeneration which takes place is

fatty, and may reach a high degree, as, for instance, in the heart of the septicaemic type. The endothelial cells, which line the blood-vessels, and the supporting cells of such organs as the liver and spleen are especially affected by the toxin liberated in the blood, and show fatty and other degenerative changes. The polymorphonuclear leucocytes in the general circulation are also markedly affected in the same manner. This degeneration is accompanied by pigmentation due to phagocytosis of the pigment granules which become free in the blood. The absorption of this pigment by certain cells, such as the stellate cells of the liver and the supporting cells of the spleen, leads to a great increase in their size, to which the general increase of such organs is largely due. Pigmented degenerate endothelial cells may also be cast off from the vessel wall and become free in its lumen. The toxic effects on the endothelial wall may become so great as to give rise to multiple haemorrhages in the white matter of the brain, where the vessels are of a comparatively primitive nature, and thus cause the coma and death of the true cerebral type. The toxic effect is especially concentrated in the brain in this type. In the septicaemic type the intense general production of toxin may also damage the endothelial wall to such an extent that haemorrhage takes place. Examples of this are the meningeal haemorrhages and those in the capsules of the kidney in Case V and the mesenteric haemorrhage in Case XI.

The changes in the tissues of the organs themselves, with the exception of those caused by haemorrhages, can all be ascribed to toxic degeneration.

1. *Brain.* The brain in both types I and II gave marked evidence of this in the form of fatty degeneration of the nerve cells. In type II this was of a more acute and intense nature than in type I, for some of the nerve cells in the former type were completely degenerate. Diffuse round-celled infiltration was also more marked in type II, showing that reaction to the toxic degeneration was greater. The accumulation of fat in the perivascular lymphatics, derived in all probability from the degenerating tissues, was conspicuous in the case of type II, but not obvious in those of type I, where on the contrary perivascular aggregations of lymphocytes showed the more chronic nature of the degeneration. Fatty degeneration of the endothelial cells of the blood-vessels was, however, most marked in type I, where the more prolonged, though less intense, toxic effect had finally given rise to haemorrhages caused by the yielding of these degenerate cells. During the course of our investigations we obtained no evidence in confirmation of the view, which has been advanced, that in cases of malaria with cerebral symptoms thrombosis of capillaries is present. Our observations have convinced us that circulatory disturbance takes the form of definite haemorrhages rather than any form of thrombosis; it is true that many capillaries, especially in the grey matter, contain red corpuscles which all have parasites within their protoplasm, and that other capillaries contain extra-corpuscular parasites free in their lumen. We have not, however, found that such capillaries differ in any other way from others which do not contain such numbers of parasites. The red corpuscles in either case are perfect in shape, the capillary wall is unaltered, and

there is no sign of the deposition of fibrin in the parasite-containing capillaries. There appears to us no justification for considering that the circulation in such vessels is obstructed, and the assumption is an unnecessary one in order to explain the pathological changes which take place. The capillaries of the grey matter show the greatest aggregation of parasites in them, yet in the cerebral type lesions are mainly confined to the white matter. In the septicaemic type, where the numbers of parasites both in the circulation and in the organs reaches a maximum, localized lesions are not to be found in the brain, but the whole organ is uniformly affected, the degeneration being explainable as a toxic change.

2. *Agonal increase of parasites.* The great aggregations of parasites in the cerebral capillaries may possibly be due to an agonal development of the parasite in this situation. The blood supply of the grey matter of the brain is the best in the body, and the development of parasites in the blood-vessels of this organ may not entirely cease when the circulation stops. Parasites in a comparatively advanced stage of the asexual cycle may complete this cycle, rupture and liberate merozoites which then invade all the neighbouring red corpuscles, or lie free in the lumen of the capillary. Certain capillaries would thus be found with every red cell containing parasites, while others contained comparatively few or none at all.

3. *Spleen.* The spleen gave evidence of toxic changes in cases of type I by the areas of degeneration which were found in the Malpighian bodies, and in cases of type II by areas of degeneration in the pulp tissue. In type III and cases intermediate between types II and III areas of degeneration occurred in the Malpighian bodies in some, and in the pulp in others. In all types, pigmentation and degeneration of the branched supporting cells were marked. The increase of size of the organ was always due to increase of the pulp, and depended partly upon the amount of blood present in it; acute congestion being most marked in type II. There was also an increase of the pulp cells themselves, which, together with the swollen and pigmented branched supporting cells, contributed mainly to the increase in size.

4. *Liver.* The liver in all types showed degeneration of liver cells. It was marked in type I, extreme in type II, but comparatively slight in type III. The separation of columns of liver cells was greatest where the degeneration was greatest, and was chiefly due to enlarged pigmented stellate cells and endothelial cells in various stages of degeneration. Degenerate cells were sometimes found lying free in the hepatic veins. The round-celled infiltration in Glisson's capsule was greatest in type I, moderate in type III, slight in type II. The amount of congestion at the centre of the lobule varied with the condition of the heart; it was great in type II, very slight in type I, and variable in type III. Degeneration of liver cells was therefore most marked in the acute septicaemic type, while round-celled infiltration was greatest in the cerebral type with its more chronic infection.

5. *Kidney.* The kidney in all types showed a greater or less degree of

cloudy swelling in the first convoluted tubules; this can be ascribed to the excretion of toxic products by these tubules. The changes varied in each group, but nothing characteristic was found. The other structures of the kidney showed little change with the exception of fat and pigment in the glomeruli and vessel walls.

6. *Heart.* The heart showed the effects of toxic degeneration in a very different manner in the three types. In type I the heart-muscle was comparatively little changed. Striation was well preserved and fatty change was confined to the undifferentiated protoplasm round the nucleus; the fibres were not fragmented. In type II the signs of acute degeneration were extreme. Fatty change was most conspicuous throughout the muscle fibres, and fragmentation of them was very extensive. Nothwithstanding these acute changes striation was still preserved to a remarkable degree, and the nuclei were little altered. The extreme degree of fragmentation found in this type in muscle fibres with well-staining nuclei and good striation supports the view that the change is a terminal one, only taking place in the agonal stage; it is, nevertheless, good evidence of very acute toxic poisoning. In type III fatty degeneration was comparatively slight, but striation was to a great extent lost, a granular change was widely spread, and the muscle nuclei were degenerate. Fragmentation was present, but was not so extensive as in type II. The changes were characteristic of a much more chronic degeneration.

7. *Stomach.* Attention was drawn to the condition of the stomach in Case I by small submucous haemorrhages, especially at the cardiac end. These were extremely common in cases of malaria; they were accompanied by the presence of a considerable amount of fat in the oxyntic cells. Whether these changes are due to the malaria or are due in part also to quinine given by the mouth is at present uncertain, but they may explain the digestive disturbances which often occur in cases of malaria under quinine treatment.

VIII. *Changes in the Cells of the Blood. Occurrence of Myelocytes.*

The changes in the blood apart from the parasites present in it are well known, and consist of a diminution in both red and white corpuscles, which may reach a high degree in chronic cases. In our experience cases with severe anaemia usually had red counts of about 3,000,000 per c.mm., while cases with no marked anaemia had counts of about 4,000,000. The leucopenia affects the polymorphonuclear leucocytes mainly. Lymphocytes are usually normal in number and large mononuclear cells are often increased. The leucocyte count averages between 5,000 and 6,000 per c.mm. The diminution in red corpuscles and polymorphonuclear leucocytes is to a considerable extent due to alterations in the blood-forming tissues, owing to the invasion of the malarial parasite, but destruction in the peripheral blood is also a factor, not only in the case of red corpuscles but also in that of the polymorphonuclear leucocytes, for pigmentation and fatty change are always to be found in them, and are often of great degree.

In cases with severe anaemia, the grave diminution in red corpuscles and polymorphonuclear leucocytes is frequently accompanied by the presence of their more undeveloped forms, and nucleated reds and polymorphonuclear myelocytes are present in the peripheral blood. We have found that the occurrence in blood-films of myelocytes is a very constant phenomenon in severe malarial anaemia, the numbers present forming about 5 to 8 per cent. of the total leucocytes. The presence of myelocytes in small numbers in a case of anaemia where malaria may be suspected considerably strengthens this supposition, and repeated films should be taken at intervals and thoroughly examined before the diagnosis of malaria is definitely negatived. We have repeatedly found the identification of myelocytes of much use in cases where malarial parasites were not at first found.

IX. *The Hiding-places of the Malarial Parasite in the Body.*

During the course of the histological investigations which we have made, we have kept before us the problem of the possible situations in which the malarial parasite lies up during the quiescent period between attacks, and have endeavoured to make a thorough search of the tissues of the organs which we have examined from this point of view. We have convinced ourselves that malarial parasites do exist in certain situations outside the general circulation. The principal organs in which we have found evidence of this are two, the spleen and the heart. We have not included the bone marrow in our investigations, and therefore cannot say whether possible places exist there or not.

In the spleen we have found the malarial parasite lying in the substance of the trabeculae entirely apart from any vessel or capillary (Fig. 6). Descriptions of this have already been given in several cases which have been described in detail. The form of the parasite is invariably the same, being always a filled-in ring with a fairly conspicuous nucleus on the periphery of the ring. Its size is that of the similar form found in the circulation, being larger and more conspicuous than the early fine ring, but not so large as the prior form; it shows no pigment. The parasites mostly lie between the fibres of the elastic and fibrous tissues, and not in any defined lymph space, though one or two have been observed which do appear to be enclosed in such a space. Parasites have also been found in the supporting cells of the spleen pulp; occasionally three or four are enclosed within one cell. Such cells are, however, almost invariably degenerate, so it is unlikely that parasites could continue to lie quiescent in them for any length of time. These branched supporting cells are highly phagocytic, as is shown by the large masses of pigment that they contain, and also by the presence of red corpuscles or other cells in their protoplasm. The presence of parasites in such cells points rather to a phagocytic engulfment, leading to the death of either the parasite or of the cell, than to any likelihood of a prolonged storage of the parasite in it.

It has also been mentioned that parasites were to be found in the stellate cells of the liver, and it is possible that they may exist in such cells for some

considerable time. It is, however, unlikely that they should exist without change in these cells over periods which would often be necessary to explain the occurrence of a particular malarial relapse. The stellate cells are also phagocytic in nature, as is shown by their power of absorbing the free malarial pigment from the circulation ; they may therefore be looked upon as comparable to the supporting cells of the spleen in their relationship towards parasites.

In the heart, parasites in the form of filled-in rings have also been found in a number of cases that we have examined ; they lie outside the circulation in two different situations, the sarcoplasm of the muscle fibres (Fig. 5), and the lymph spaces between the fibres. The relationship of the capillaries supplying the heart-muscle with the contractile muscle-fibres is extremely intimate, so that the greatest care had to be exercised to eliminate the possibility that a given parasite was lying in a fine capillary crossing the particular muscle fibre. We therefore did not hold the identification of the parasite within the muscle to be established, until we had substantiated its presence there both in longitudinal and transverse section. The parasite always lay close against the nucleus of the muscle fibre in the spindle-shaped sarcoplasm which surrounds it. This tissue was always marked off from the contractile substance around it by the comparatively large globules of fat which were present in all cases we examined. In longitudinal section the parasites have been found lying at exactly the same focal level as the nucleus, and in cross-section lying in the sarcoplasm entirely surrounded by contractile tissue. We therefore hold that it is justifiable to consider that they actually lie inside the muscle fibre. Spaces between fibres were considered to be lymph spaces when no sign of any separate endothelium could be found, and the space was bounded only by the outer edge of the muscle fibres themselves. Parasites in the filled-in ring form were definitely observed in such spaces.

In addition to the muscle fibres of the heart it is quite possible that parasites may lie up in other muscle fibres, both in the unstriped muscle of the internal organs and of the arteries, and even in the striped voluntary muscle. If this is the case the possible storage place, in which the parasite could lie, comprises the greater portion of the human body. The difficulty of elimination of the parasite and the long period of time in which it could remain quiescent would then be explained.

We are ourselves inclined to the view that striped voluntary muscle is the principal store-house of the resting parasite, but further investigation on this subject is needed. We consider that the proved presence of parasites in the fibres of the heart-muscle distinctly points to such a possibility.

X. *The Evolution of the Crescent in the Brain of the Cerebral Type.*

The following is a description of certain forms of the parasite, which were found in numbers in the brain smears of Case II, and confirmed by similar smears from Case I.

Films were taken from the punctiform haemorrhages in the internal capsule.

By gentle squeezing of the brain substance enough blood was obtained for the smear. Crescents both completely developed and still immature were numerous, as many as five or six occasionally being found in one field. 100 parasites were counted at random over the slide, the ring forms being omitted, and the result obtained was as follows:

Adult male crescents	21 per cent.
„ female „	7 „ „
Immature male crescents	37 „ „
„ female „	15 „ „
Transitional forms	20 „ „

The ordinary ring forms were numerous. Male crescents were thus present in greater numbers than female crescents, the proportion being 58 to 22. The forms tabulated as transitional were intracorpuscular, varied in size and also in shape from round to oval; they had the same blue ground as the crescent with Leishman's stain, and contained pigment granules scattered promiscuously throughout their substance. On the supposition that these were forms which were in the process of development from ring to crescent, an attempt was made to trace the evolutionary cycle, and Figs. 7 to 20 represent the result. They have not been drawn to scale, but the proportion in size between the parasites and the red blood corpuscles has been kept as accurately as possible.

Fig. 7 represents the beginning of crescent formation; the plasmodium shows a complete ring of granules with particles scattered within it. The nucleus is no longer distinct, but the outer edge of the ring stains darker than the central portion. In Fig. 8 the plasmodium has a round shape, stains uniformly pale blue, and has distinct pigment particles scattered throughout its substance. An indication of the ring form still persists in the distinctly darker outline of the plasmodium. Figs. 9 and 10 show a more advanced stage; the whole plasmodium is uniformly light blue in colour, and has well-marked pigment particles scattered throughout it. The relative size of parasite and red corpuscle differs considerably in these two figures. The larger parasite, which nearly fills the whole cell, Fig. 9, is the transitional form of the male crescent; the smaller parasite shown in Fig. 10 is the transitional form of the female. The next stage in development is the gradual change in shape from round to oval shown in Figs. 11 and 12. The red corpuscle is still distinct, but the pigment is more conspicuous, though there is as yet no distinctive arrangement of its particles. Fig. 11 represents a further stage in the development of the male parasite, shown in an earlier stage in Fig. 9, and Fig. 12 represents a further stage of the female parasite shown in Fig. 10. It will be seen that the male parasite is relatively to its enclosing cell larger than the female. Fig. 13 shows pointing of one end of the larger male parasite. A further example of this is seen in Fig. 14, which is held from its proportionate size to be a still further development of the female. A ring is also shown in Fig. 13 in a corpuscle lying next to the immature male crescent, and illustrates the relative sizes of the two stages. Figs. 15 and 16 represent the male and

FIG. 7.

FIG. 8.

FIG. 9.

FIG. 11.

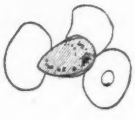

FIG. 13.

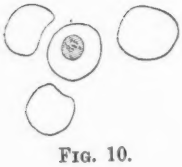

FIG. 10.

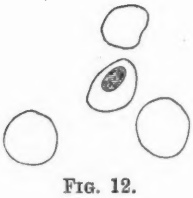

FIG. 12.

FIG. 14.

FIG. 15.

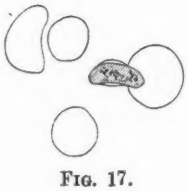

FIG. 17.

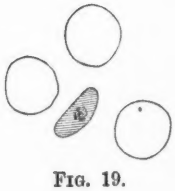

FIG. 19.

FIG. 16.

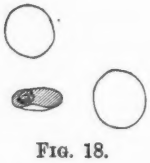

FIG. 18.

FIG. 20.

FIGS. 7–20. Stages in the development of the crescent from the ring form, from films of the brain of Case II from the 'true Cerebral' group. The relative size of red corpuscle and parasite is shown in all the figures. The detailed description of them is given in the text on pp. 423 and 425. Zeiss, Ocular 4, Objective $\frac{1}{12}$. Reduced $\frac{2}{3}$.

female respectively in which the corpuscular element is no longer visible; they are still immature and have not yet assumed the true crescentic shape. Figs. 17 and 18 represent the more mature form of male and female in which the final crescentic shape is becoming evident, and in which a distinctive arrangement of the pigment is evolving. A trace of the corpuscular envelope is still to be seen. In the male, Fig. 17, the pigment is beginning to concentrate into a central zone, while in the female, Fig. 18, a more complete concentration into the form of a ring is taking place. Figs. 19 and 20 represent mature male and female parasites. The male is larger, more blunt at the ends, less crescentic in shape, and has its pigment arranged in a diffuse central mass. The female is smaller, sharper at the ends, more crescentic in outline, and has its pigment very definitely concentrated into a central ring. The differentiation of the male and female parasite can be made in a comparatively early stage owing to their relative difference in size.

XI. *Conclusions.*

1. The pathological changes of malignant malaria depend upon the toxin liberated by the parasite. This chiefly affects the endothelium of the blood-vessels and the tissues of certain organs, especially the brain, heart, liver, and spleen.

2. The pathological processes which lead to death are of three kinds, which correspond with very definite clinical types.

3. The first, or true cerebral type, is characterized by signs of definite cerebral lesion and paralysis consequent thereon. The lesions found are definite haemorrhages in the white matter due to fatty degeneration of vessel walls. The brain has here assumed the function, usually associated only with the spleen and bone marrow, of manufacturing all forms of the malignant parasite in numbers. There is no great general increase of the malignant parasite throughout the body.

4. The second, or septicaemic type, is associated with an intense general toxaemia, which is manifested in the brain by signs of cerebral irritation, leading on to coma, and in the heart by final rapid dilatation and failure. This toxaemia is due to a rapid general increase of the parasite, owing to development of the asexual cycle throughout all organs of the body and also in the peripheral blood.

5. The third, or cardiac type, is characterized by signs of heart failure only, without cerebral manifestations. The heart failure is caused by chronic degeneration of the heart-muscle, to which is added a terminal general invasion of the body similar to that of type II, but of much milder degree.

6. Intermediate forms, in which the factors present in types II and III both play a part, are also found.

7. Treatment in cases of type I is of no avail, and no warning signs of the approach of the condition have been discovered.

8. Treatment in cases of type II, when the clinical condition is fully established, is too late to be of much value; ample warning of the approach of

the condition can, however, be obtained by the method of parasite counts, and treatment begun at this stage affords every prospect of success.

9. The limit of safety is 5,000 parasites per c.mm. Any count higher than this calls for the immediate administration of energetic treatment with intravenous quinine. The occurrence of the more advanced stages of the asexual cycle in the peripheral blood, even when the general count is low, also calls for similar treatment.

10. The treatment in cases of type III should be directed to the cardiac condition, but the parasite count should also be watched. The condition of the heart never contra-indicates the administration of quinine, as a terminal septicaemic condition is the chief danger to be feared. In cases with great enfeeblement of the heart the latter need be of only very mild degree to cause a fatal termination.

11. Polymorphonuclear myelocytes are almost always present in the peripheral blood in the severe anaemia of chronic malignant malaria; their identification is of value when no parasites are to be found.

12. The malignant parasite has been found in certain situations, which are of importance, as they indicate places where the parasite may be stored up in quiescent periods between attacks. The chief of these is the undifferentiated protoplasm around the nucleus of the cardiac muscle fibre. The suggestion is made that parasites may be similarly stored in unstriped muscle and even in striated voluntary muscle. They have been also found in the fibrous tissue of the trabeculae of the spleen and in the supporting cells of the spleen and liver. The importance of the last two situations is, however, doubtful from the point of view of storage. The form of the parasite in these situations is always the filled-in ring.

13. The complete cycle of development of the crescent from the ring has been followed in the brain of fatal cases of the true cerebral type.

We desire to express our deep indebtedness to Lieutenant-Colonel Brakenridge for giving us every facility and encouragement in carrying out these observations, and to Lieutenant-Colonel Greenwood for continuing this assistance and encouragement.

To Major Wiltshire our thanks are especially due for his never-failing interest and co-operation. To Captain Herklots and our other brother officers we are also greatly indebted for much valuable assistance.

TETANY AND THE ADMINISTRATION OF ALKALIS

By P. S. HENDERSON

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DURING recent years there has been much search after the exciting factor which causes the symptoms and increased electrical excitability of tetany. MacCallum (1) referred the condition to a diminished calcium content of the blood and tissues, while Noël Paton and Findlay and their co-workers (2) hold that the pathological change is of the nature of guanidin poisoning.

In 1915 Wilson, Stearns, and Janney (3) stated that alkalis were known to increase the symptoms of tetany, and, on the other hand, that by the administration of acids per os to parathyroidectomized dogs they had been successful in keeping the symptoms in abeyance until the presentation of bicarbonate of soda. Unfortunately, however, only one of the numerous animals so experimented with retained the hydrochloric acid in sufficient quantity, but they nevertheless considered themselves justified in their conclusions. These authors (4) state in a subsequent paper that at certain stages of tetania parathyreopriva there is an increased alkalinity of the blood, a condition to which they give the name 'alkalosis'.

Later, Howland and Marriott (5) 'made determinations of the hydrogen ion concentration of the serum of infants with tetany by the dialysis indicator method', but they did not find an alkalosis. They state, however, that it is not unusual to see the symptoms of tetany develop in cases of acidosis treated with bicarbonate of soda. They give records of three children of nine months, three years, and four and a half years of age, suffering from acidosis, in whom respectively 4·2 grm., 13 grm., and 32 grm. of sodium bicarbonate induced carpopedal spasm and increased electric excitability, and in whom all the symptoms disappeared on the withdrawal of the alkali. In all these cases there resulted, in addition to the clinical manifestations of tetany, a diminution of the calcium content of the blood serum. In one the hydrogen ion concentration of the serum was determined $-7{\cdot}6$, then in acidosis $-6{\cdot}8$.

Dr. Leonard Findlay, of the Royal Hospital for Sick Children, Glasgow, informed me that he had seen no such accidents as the result of the administration of even large doses of bicarbonate of soda in severe cases of enteritis and pyuria, but that he had no definite results to quote, and he suggested that I should investigate the question.

In commencing this investigation the question of what justifies a diagnosis of tetany has to be faced. In the presence of active tetany the answer is simple, but in its absence we are thrown back on the signs of latent tetany, viz. mechanical and electrical excitability (E. E.) of the peripheral nerves. Concerning the reliability of these diagnostic signs, there is some difference of opinion. The original dictum of Thiemich that a K. O. C. (cathodal opening contraction) with less than 5 m. a. in itself signifies tetany has of late not been considered sufficiently comprehensive, and has given place to the view of von Pirquet that when the A. O. C. (anodal opening contraction) is less than the A. C. C. (anodal closing contraction) tetany exists. As a result of extensive tests in animals before and after tetania parathyreopriva, Noël Paton and Findlay showed that before the development of the symptoms, i.e. in the normal animal, the A. O. C. was frequently less than the A. C. C., and therefore they concluded that as a sign of tetany this qualitative alteration in the E. R. (electrical reactions) could not be depended upon. In their experience the increased excitability of the K. O. C. and the K. C. C. were the striking features.

In clinical tetany, excepting immediately after a convulsion, the facial phenomena (F. P.) seems, however, to be the most reliable indication, and in the present investigation we have taken as indication of tetany the presence of a F. P., and the obtaining of a K. O. C. with a current of less than 5 m. a.

Our material consisted of nineteen children varying in age between eight weeks and eleven years, convalescent or suffering from different diseases. In some cases the E. E. was tested for several days before the administration of the alkali, while in others the alkali had been given for some time before the investigation was commenced. Many observations were made in each case, sometimes every day, sometimes every other day, but occasionally only at longer intervals.

The following are details of the cases examined:

Case I. T. A., male, aged 8 weeks. Admitted 8.5.19. Diagnosis—pylorospasm.

Date.	K. C. C.	A. C. C.	A. O. C.	K. O. C.	Remarks.
19.5.19	1·0	2·5	4·9	5+	
23.5.19	1·7	2·3	4·5	5+	4 grm. S. B.[1] daily
25.5.19	1·1	2·5	4·5	5+	
29.5.19	0·8	1·3	1·0	5+	Severe vomiting, S. B. discontinued
1.6.19	0·8	2·5	4·0	5+	

Case II. J. M., female, aged 4½ months. Admitted 21.10.18. Diagnosis—pyelonephritis (with fever).

Date.	K. C. C.	A. C. C.	A. O. C.	K. O. C.	Remarks.
22.11.18	1·5	2·5	3·0	5+	8 grm. S. B. daily from 12.11.18
23.11.18	1·6	2·0	4·0	5+	
25.11.18	1·8	2·0	4·0	5+	
30.11.18	1·6	2·3	4·0	5+	
3.12.18	1·6	2·2	4·0	5+	

[1] Sodium bicarbonate.

Case III. W. L., male, aged 5½ months. Admitted 25.9.18. Diagnosis—diarrhoea.

Date.	K. C. C.	A. C. C.	A. O. C.	K. O. C.	Remarks.
7.12.18	1·1	1·5	4·0	5+	
9.12.18	1·5	1·8	5·0	5+	12 grm. S. B. daily
11.12.18	1·6	2·6	5·0	5+	Severe vomiting, S. B. discontinued
13.12.18	1·1	2·4	5·0	5+	

Case IV. M. C., female, aged 6 months. Admitted 21.8.19. Diagnosis—pyelitis.

Date.	K. C. C.	A. C. C.	A. O. C.	K. O. C.	Remarks.
7.9.19	0·7	1·5	1·5	5+	Bis. carb. } 4 grm. daily Sod. carb. }
11.9.19	0·6	1·1	2·5	5+	
15.9.19	0·6	3·2	2·0	5+	

Case V. A. A., female, aged 8 months. Admitted 17.8.19. Diagnosis—pyelitis.

Date.	K. C. C.	A. C. C.	A. O. C.	K. O. C.	Remarks.
6.9.19	0·8	2·3	5·0	5+	S. cit. } 4 grm. daily since S. bic. } 29.8.19
10.9.19	0·9	2·9	2·4	5+	
15.9.19	1·1	1·6	5·0	5+	

Case VI. D. C., male, aged 8 months. Admitted 21.11.18. Diagnosis—pyuria.

Date.	K. C. C.	A. C. C.	A. O_4 C.	K. O. C.	Remarks.
25.11.18	0·8	2·3	3·0	5+	
26.11.18	0·9	2·0	2·0	5+	4 grm. S. B. daily
27.11.18	1·7	2·5	2·5	5+	
28.11.18	1·4	2·2	2·5	5+	
2.12.18	1·2	2·4	3·0	5+	

Case VII. E. C., female, aged 14 months. Admitted 18.11.18. Diagnosis—diarrhoea.

Date.	K. C. C.	A. C. C.	A. O. C.	K. O. C.	Remarks.
7.12.18	1·5	1·7	5·0	5+	
9.12.18	1·5	1·7	5·0	5+	12 grm. S. B. daily
11.12.18	1·4	1·9	5·0	5+	Severe vomiting, S. B. discontinued

Case VIII. B. G., female, aged 16 months. Admitted 27.10.18. Lobar pneumonia.

Date.	K. C. C.	A. C. C.	A. O. C.	K. O. C.	Remarks.
7.12.18	1·4	3·5	3·5	5+	Convalescent
9.12.18	1·2	3·1	3·2	5+	12 grm. S. B. daily
11.12.18	1·1	3·7	4·0	5+	Severe vomiting, S. B. discontinued

Case IX. B. S., female, aged 1 year. Admitted 25.7.19. Diagnosis—pyelitis.

Date.	K. C. C.	A. C. C.	A. O. C.	K. O. C.	Remarks.
10.9.19	0·6	0·9	1·9	5+	4 grm. S. B. daily since 9.9.19
11.9.19	—	—	—	—	S. B. increased to 5 grm. daily
15.9.19	0·6	3·2	3·9	5+	

Case X. R. F., female, aged 3 years. Admitted 23.11.18. Diagnosis—goitre.

Date.	K. C. C.	A. C. C.	A. O. C.	K. O. C.	Remarks.
28.11.18	1·5	1·3	2·5	5+	
2.12.18	1·2	1·3	2·5	5+	
4.12.18	1·1	0·9	2·5	5+	12 grm. S.B. daily
5.12.18	1·4	1·7	2·5	5+	
7.12.18	1·5	1·6	2·5	5+	
9.12.18	1·4	1·6	2·5	5+	Dose of S. B. increased to 15 grm. daily
11.12.18	1·3	1·1	2·5	5+	
13.12.18	1·3	1·4	3·0	5+	Dose of S. B. increased to 18 grm.
16.12.18	1·3	1·4	3·0	5+	
18.12.18	1·1	1·4	3·0	5+	
20.12.18	1·2	1·2	3·0	5+	

Case XI. J. C., male, aged 3 years 11 months. Admitted 8.10.18. Diagnosis—?

Date.	K. C. C.	A. C. C.	A. O. C.	K. O. C.	Remarks.
28.11.18	2·5	4·0	5·0	5+	
2.12.18	2·6	4·3	5·0	5+	
4.12.18	2·5	4·2	5·0	5+	12 grm. S. B. daily
5.12.18	2·2	3·5	5·0	5+	
7.12.18	2·3	4·0	5·0	5+	

Case XII. R. C., male, aged 4 years 6 months. Admitted 7.11.18. Diagnosis—lobar pneumonia.

Date.	K. C. C.	A. C. C.	A. O. C.	K. O. C.	Remarks.
13.12.18	1·1	1·9	3·0	5+	Convalescent
16.12.18	1·5	2·0	2·6	5+	9 grm. S. B. daily
18.12.18	1·8	2·0	2·5	5+	
20.12.18	1·5	2·5	1·4	5+	Sick after each dose
21.12.18	1·5	2·3	3·5	5+	
27.12.18	1·1	2·0	2·5	5+	

Case XIII. S. K., female, aged 5 years. Admitted 16.8.18. Diagnosis—pyelonephritis.

Date.	K. C. C.	A. C. C.	A. O. C.	K. O. C.	Remarks.
21.11.18	1·0	1·8	4·0	5+	8 grm. S. B. daily
22.11.18	1·0	2·0	4·0	5+	
23.11.18	1·0	2·1	4·5	5+	
26.11.18	1·1	1·9	4·5	5+	
30.11.18	1·2	2·3	3·6	5+	
3.12.18	1·4	2·4	3·5	5+	

Case XIV. M. D., female, aged 5 years 6 months. Admitted 27.11.18. Diagnosis—diarrhoea.

Date.	K. C. C.	A. C. C.	A. O. C.	K. O. C.	Remarks.
4.12.18	0·8	1·1	2·5	5+	12 grm. S. B. daily
7.12.18	0·8	1·5	2·3	5+	
9.12.18	0·9	1·4	2·2	5+	
13.12.18	0·8	1·3	2·5	5+	
20.12.18	0·8	1·1	2·8	5+	
23.12.18	0·8	1·1	2·8	5+	
27.12.18	0·9	1·2	2·5	5+	

Case XV. J. McC., female, aged 6 years. Admitted 18.11.18. Diagnosis—diarrhoea.

Date.	K. C. C.	A. C. C.	A. O. C.	K. O. C.	Remarks.
7.12.18	1·4	2·0	3·0	5+	
9.12.18	1·3	2·5	3·0	5+	18 grm. S. B. daily
11.12 18	0·9	1·7	2·0	5+	
13.12.18	1·1	2·0	3·0	5+	
16.12,18	1·7	2·1	3·0	5+	

Case XVI. R. W., female, aged 8 years 6 months. Admitted 4.12.18. Diagnosis—subacute rheumatism.

Date.	K. C. C.	A. C. C.	A. O. C.	K. O. C.	Remarks.
13.12.18	0·9	2·1	1·0	5+	Sod. salicyl., 10 grains six times daily since 7.12.18
16.12.18	1·2	2·4	1·7	5+	
18.12.18	1·3	3·8	2·1	5+	
20.12.18	0·9	3·0	1·3	5+	18 grm. S. B. daily in addition to above
23.12.18	1·1	3·5	1·8	5+	
27.12.18	1·2	3·8	2·5	5+	

Case XVII. S. B., female, aged 9 years. Admitted 6.11.18. Diagnosis—cough.

Date.	K. C. C.	A. C. C.	A. O. C.	K. O. C.	Remarks.
13.12.18	1·9	3·0	3·2	5+	
16.12.18	1·4	1·9	2·5	5+	18 grm. S. B. daily
18.12.18	1·1	1·8	1·7	5+	
20.12.18	1·1	1·8	1·6	5+	
23.12.18	1·5	1·8	2·3	5+	
27.12.18	1·4	1·5	2·5	5+	

Case XVIII. E. J., female, aged 10 years. Admitted 29.10.18. Diagnosis—thrombosis of cerebral vessels—syphilis.

Date.	K. C. C.	A. C. C.	A. O. C.	K. O. C.	Remarks.
2.12.18	1·6	2·1	2·5	5+	
4.12.18	1·4	2·0	2·2	5+	12 grm. S. B. daily since 31.12.19
5.12.18	1·0	1·7	2·6	5+	
7.12.18	1·4	2·2	2·7	5+	

Case XIX. M. F., female, aged 11 years. Admitted 23.8.19. Diagnosis—pyuria.

Date.	K. C. C.	A. C. C.	A. O. C.	K. O. C.	Remarks.
7.9.19	0·7	1·3	3·7	5+	Pot. cit. 4 grm. Sod. bic. 4 „ } daily
11.9.19	0·6	1·5	1·7	5+	
15.9.19	1·0	1·3	2·2	5+	

None of the cases showed any sign of carpopedal spasm or of the facial phenomenon. In no case was a K. O. C. obtained with a current of less than 5 m. a. In three cases (Nos. *I*, *XII*, and *XVII*), however, there was observed on one or two occasions, after the administration of large doses of the alkali, a von Pirquet reaction, i.e. the A. O. C. was obtained with a less current than the A. C. C.

From the above results it will be seen that in not a single instance could a definite diagnosis of tetany be made, although in some cases as much as

120 grm. of bicarbonate of soda were administered during a period of seven days. In the three cases quoted by Howland and Marriott, the largest dose was 32 grm. in one week in the case of a child of 4 years and 3 months.

The doses given by Howland and Marriott varied from 0·138 grm. per kilogram of body weight in twelve hours, to 0·84 grm. per kilo. In one of their cases the symptoms became manifest within twelve hours, while in another they observed signs of tetany only after seven days' treatment.

Our doses varied from 0·12 grm. per kilo of body weight in twelve hours to 0·92 grm. per kilo, the alkali being given in some cases for as long as twenty-three days.

This investigation therefore lends no support to the idea that symptoms of tetany may result from the administration of large quantities of alkali.

I have to thank Dr. Leonard Findlay, at whose instigation this work was started, for help and advice; and my thanks are also due to Miss Vaughan, who assisted me throughout in the taking of the electrical reactions, and to Dr. Paterson, who made the observations in three of the cases quoted.

This work was done under the auspices of the Medical Research Committee.

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ADULT TETANY AND METHYLGUANIDIN: A METABOLIC STUDY

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The chief interest in this case does not centre round the fact of it being one of adult tetany, which is nevertheless comparatively rare in this country, but depends on the fact that we were given facilities for making a study of the metabolism such as had been already carried out by Burns and Sharpe in this laboratory both in infantile tetany and in experimental tetania parathyreopriva. In both of these conditions a great increase in the amount of guanidin excreted by the urine was observed, and in experimental tetania parathyreopriva an increase of the guanidin in the blood was found to exist.

From these results and from their study of the action of guanidin salts, Noël Paton and Findlay (1) concluded that the symptoms in both these conditions are due to an increased production of guanidin as the result of some alteration in metabolism.

As will be seen from the results of the investigation of the metabolism recorded below, in this case of adult tetany there was also an excessive excretion of guanidin by the urine. The amount of guanidin in the blood, even after parathyroidectomy, is so small that it is not feasible to carry out examinations for this substance in the blood of the human subject.

Case.

M. H., female, unmarried, aged 52 years. According to her own and her mother's accounts, she was apparently a very healthy infant and young child, but at the age of eighteen months she developed a severe illness, called 'marasmus of the bowels' (? coelic disease), which lasted for six years. Since then she has never been well. She was confined to bed for three years and later, on going to school, developed curvatures (rachitic) of the legs. At the age of 18 years she commenced to suffer from spasms in the hands, which ever since have continued to trouble her during the spring and autumn and in cold weather, but not during the summer. These spasms were mainly limited to the hands, but at times they spread to the facial and respiratory muscles, and caused her not only great alarm, but also, at times, danger to life. Nevertheless, her general health was tolerably good, though she could not be described as robust. At no time of her life did she weigh more than six stones.

The patient first came under the notice of Dr. R. O. Adamson, Glasgow, in 1907, and we are indebted to him for many of the clinical and historical details. At that time she complained of general debility, languor, loss of appetite, and the attacks of spasms in the hands previously mentioned. She was small, obviously frail, markedly knock-kneed, and weighed in her clothes 5 st. 8 lb. Carpopedal spasm could be induced by compression of the arm—Trousseau's sign.

For some time general treatment relating to diet, exercises with courses of massage, and sedative drugs kept her in comparative comfort. Since 1916, however, her condition has become worse. During that year she had a very severe and prolonged attack of tetany.

In the summer of 1917, while on holiday in the Highlands of Scotland, she developed a severe attack of diarrhoea, and since then her bowels have moved rather frequently, the motions being large, light grey in colour, and greasy. She presented at this time all the symptoms of great debility. X-ray examination of the stomach revealed it to be situated slightly higher up and more transversely than usual: the bismuth test meal was found to leave the stomach readily, and to pass rapidly through the intestines, reaching the sigmoid flexure within five hours. At this time also the stools were tested for pancreatic efficiency. She was kept on a Schmidt diet for several days previous to the examination of the stools, which is reported to have disclosed complete absence of pancreatic secretion. The urine gave marked indican reaction.

In October 1917 she had another very severe attack of tetany implicating the face and respiratory muscles. Bromides and chloral were administered, but at times the condition was so alarming that ether was employed and pushed to mild anaesthesia.

She came under the notice of one of us (L. F.) in May 1919. Her general health had deteriorated, and the attacks of tetany, though on the whole not so severe, had become more frequent. She was much emaciated, with considerable pigmentation of the exposed skin of the face and hands. She showed an extreme degree of double knock-knee and her chest presented a slight rosary. The facial phenomenon was marked and Trousseau's sign was present. The electrical reactions tested in the right ulnar nerve gave: K. C. C. = 0·2 m. a., K. O. C. tetanus with 3·0 m. a. Physical examination was otherwise negative.

Metabolic Study.

At this time the patient was put on a special diet for six days. This consisted of bread and butter, biscuits, and milk, and was controlled in the following manner. Two identical meals were prepared; one was consumed, and the other, along with a sample of the milk, was sent to the laboratory and there weighed and retained for examination. The bowels, fortunately, moved regularly daily during the period of study and urine and faeces were collected each day. We are convinced that, although during this period the patient remained in her own house, we were successful in obtaining all the excreta. The metabolism of calcium was investigated and the urine examined for the presence of guanidin.

Major Hutchison, I.M.S. (2), made some examinations of the digestion and absorption of fats by the methods already described by him, and he reported no increase in the splitting of fats, but a distinct decrease in their absorption. Unfortunately his departure for India prevents our giving his figures.

The following are our results:

Daily Excretion as Dimethylguanidin.

Day.	Daily Quantity of Urine.	Daily Amount of Dimethyl-guan.	% of Dimethyl-guan.	Nitrogen.	M. P.	Calculated Nitrogen.	Calculated M. P.
	c.c.	grm.					
1	916	0·175	0·019	28·7	227° C.	26·5	225° C.
4	900	0·083	0·009	29·4	227° C.	26·5	225° C.

The smaller excretion of dimethylguanidin on the fourth day of the study may be due to the decreased intake of proteins upon the restricted diet.

CaO Metabolism.

Day of Observation.	Daily Weight of Dry Faeces.	CaO in 1 grm.	Intake of CaO per day.	Excretion of CaO per day.	CaO retained per day.	% CaO retained per day.	A/B Factor (see p. 436).	
	grm.		grm.	grm.	grm.			
2	29	0·039	2·04	1·04	1·00	49·0	27·8	
4	20	0·050	2·02	1·00	1·02	50·5	20·0	
6	33	0·045	2·08	1·47	0·61	29·3	22·5	
8	88	0·040	4·01	3·52	0·49	12·2	25·0	
	42·5	0·043	2·53	1·75	0·78	35·2	23·8	Average
	88	0·050	4·01	3·52	1·02	50·5	27·8	Maximum
	20	0·039	2·02	1·00	0·49	12·2	20·0	Minimum

Four alternate days were taken over a period of eight days' study. The faeces were so bulky in the moist condition that we were unable to deal with the excreta over the whole period.

Since all the urine was used for the determination of the dimethylguanidin, the calcium excreted by the urine is not included in the table. Less than 20 per cent. of CaO intake is excreted by the urine in a normal adult.

Normal Adults (Four Cases on a Fixed Diet [1] for Seven Days).

Weight of Dry Faeces per day.	Intake of CaO per day.	Excretion of CaO per day.	CaO retained per day.	% CaO retained per day.	A/B Factor.	
grm.	grm.	grm.	grm.			
40·2	1·49	0·57	0·92	61·7	74·3	Average
47·9	1·64	0·81	1·22	74·5	92·8	Maximum
36·1	1·31	0·42	0·70	46·5	59·1	Minimum

Conclusions.

In this case of adult tetany there were:

1. An increased excretion of guanidin by the urine, just as in the case of infantile tetany and tetania parathyreopriva, but in this case it was chiefly in the form of dimethylguanidin.

2. A subnormal retention of calcium.

3. A diminished absorption of fat, a point previously observed in infantile tetany.

[1] Chiefly of bread and milk [Burns and Sharpe (3)].

4. No deficiency in fat splitting and consequently no impairment of the pancreatic function.

This work was done under the auspices of the Medical Research Committee. J. S. Sharpe is responsible for the chemical analyses.

Appendix.

Methods.

A. *Urine.* One litre of the urine, preserved with thymol and chloroform as soon as passed, was treated with a slight excess of 5 per cent. tannic acid. The precipitate was allowed to settle and filtered through a Buchner filter. To the filtrate saturated barium hydrate solution was added until no further precipitate occurred and the supernatant liquid became green. The precipitate was then filtered off and the barium in the filtrate removed by a slight excess of 5 per cent. sulphuric acid. The excess of sulphuric acid was then removed by a cream of barium carbonate and water and the whole settled and filtered. The filtrate was made slightly acid with hydrochloric acid and concentrated to a syrup. The syrup was then extracted with absolute alcohol and filtered and washed with alcohol, the filtrate again evaporated and again extracted with alcohol.

Under this treatment the inorganic bases remain insoluble.

The filtrate was evaporated to about 100 c.c. The guanidin compounds were precipitated from a 50 per cent. aqueous alcohol solution by aqueous alcoholic solution (1 part to 1 part) saturated with picric acid.

Crystals appeared within a few minutes of adding the picric acid solution. The crystals were in the form of needles and plates of a bright yellow colour. They were very regular in size and shape and there was no indication that any base other than guanidin was present.

The nitrogen and melting-point were determined in the crystals from two days in the period of study.

As the composition of the picrate was nearest that of dimethylguanidin the results were calculated as such.

B. *CaO Metabolism Method.* The method employed in the calcium metabolism studies will be published in a future paper. The same procedure, however, was used in this case. Generally this may be stated thus:

(1) Collection of whole of faeces. (2) Drying on steam bath until constant in weight. (3) Weighing and grinding the whole daily amount. (4) Analysis of a known weight of the sample for the CaO content, finishing by titration with $\frac{N}{10}$ potass. permanganate.

The A/B factor is obtained by dividing the weight of dried faeces per day by the daily excretion of CaO.

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